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Economic Evaluation of Antenatal Screening for Down Syndrome and Serious Congenital Heart Defects in Norway

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Table of contents

Declaration of non-plagiarism.....	3
Acknowledgements	4
List of abbreviations.....	5
1 Introduction	6
2 Literature review	13
3 Methods	30
4 Results	38
5 Discussion	49
6 Conclusion.....	63
References	67
Appendix	77

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The responsibility for any errors or omissions remains, of course, with me.

Oslo, February 3, 2010

Espen Movik

List of abbreviations

CB	Combined strategy
CP	Comprehensive strategy
CU	Current strategy
DS	Down syndrome
GBP	Great British Pounds sterling
MNOK	million Norwegian kroner
NOK	Norwegian kroner
PPV	positive predictive value
PTR	positive test rate
SEK	Swedish kroner
SCHD	Serious congenital heart defects
USD	United States Dollars

1 Introduction

Background

Following recommendations laid down by a consensus conference in 1986, the policy of the Norwegian government has been to offer a routine ultrasound scan to all pregnant women at 18 weeks of gestation, i.e. in the second trimester (weeks 14-27) of pregnancy (1). This form of antenatal screening is also provided in other European countries, though several countries have gone further and now offer universal screening in the first trimester (weeks 1-13), between the 11th and 13th week of gestation, as well as in the second (2). In 2006, the Norwegian Directorate for Health contemplated a revision of its antenatal care guidelines, and in the process, sought to determine whether an expansion of the programme to incorporate universal first trimester screening would be a rational step with regard to the anticipated extra benefits and costs. Except for a relatively small patient co-payment charge, antenatal screening is publicly financed as is the case with most other health services. Norway has however, a small but thriving private health care sector, and first trimester ultrasound scanning has been offered by private providers in recent years.

There are many potential benefits of antenatal ultrasound screening and some of them are undoubtedly controversial. The information gained from a scan may, depending on its timing, assist in determining the pregnancy term, the number of foetuses in the uterus, the location of the placenta and the condition of the foetus. If the foetus is found to suffer from a particular disease, it may sometimes be treated prior to birth (3). Invariably however, ultrasound scanning in pregnancy is often associated with the detection of foetal anomalies or defects, such as Down syndrome, congenital heart defects or neural tube defects. The detection can in some cases lead to the pregnancy being terminated, whilst in other cases it may prepare the parents for a life with a child who may require more attention and care than others. This provision of information may be considered beneficial, however one may choose to act upon it, although it also invites an active decision which could induce negative feelings. On the other hand, the potential stress and anxiety involved in the screening and diagnostic process may be viewed as disadvantageous (4). This study will focus on two of the most important anomalies, at least in terms of the attention they are given in the literature: Down syndrome (DS) and serious congenital heart defects (SCHD).

The conditions

Down syndrome

Down syndrome, also known as trisomy 21, is caused by a fertilized egg having three copies of chromosome 21 rather than two. The condition may be mild or severe, but is generally characterized by slower than normal physical and mental development.(5). The disease is associated with mild to moderate mental retardation, though many children with Down are able to lead a close to normal life, with varying degrees of assistance required, for example in the form of speech or physical therapy or extra tuition.

The prevalence of Down syndrome in Norway was found by Melve and colleagues (6) to be 2.0 per 1 000 among the 288 213 births and terminations recorded in the Medical Birth Registry of Norway in the period 2001-2005. Risk tends to increase with maternal age (7;8) and the results of screening studies will therefore be dependent upon the age composition of the population studied. In Norway the watershed high-risk mark in terms of age stated in guidelines for antenatal care is 38, whilst in other countries it may be 35 (reference).

The screening alternatives relevant to the present analysis are as follows. In the first trimester, measurement of nuchal translucency in ultrasound screening is, together with maternal age, employed to calculate the risk of Down syndrome. Nuchal translucency (NT) refers to the thickness of the fluid collected behind the neck of the foetus (reference BMJ), which is only present for a short time, between weeks 10 and 14 of gestation, and may signal the presence of disease or foetal immobility. In addition to ultrasound with NT, a blood sample can be taken to test for two serum hormone markers; human chorionic gonadotrophin (hCG) and pregnancy-associated plasma protein (PAPP-A) which are indicative of chromosomal defects such as Down syndrome. Together, the ultrasound and the serum test are sometimes referred to as the combined test or the double test. If the risk of Down syndrome is considered to be significantly large, the invasive follow-up test known as chorionic villus sampling is warranted. In the second trimester routine ultrasound scan, the operator investigates so-called soft markers, which are minor anatomical variations that, combined with maternal age, are used to assess the risk of chromosomal anomalies (9). If the risk is deemed to be high, presence or absence of the anomaly can be confirmed by means of an invasive test known as amniocentesis.

Serious Congenital Heart Defects

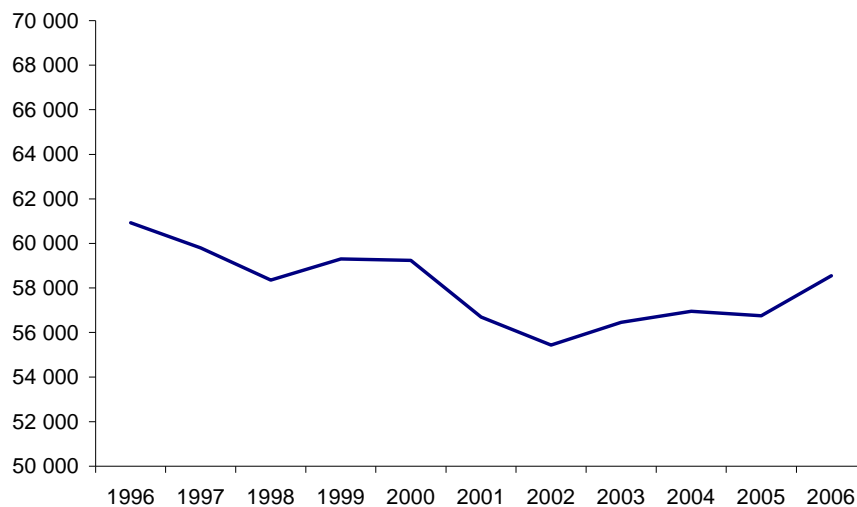
Serious, major or critical congenital heart disease (SCHD) differs from other congenital heart defects by being associated with high mortality rates, although these can sometimes be treated, either *in vitro* or with long-term follow-up (10). The incidence of these conditions accounts for around half of all detected cases of congenital heart defects (10). They may involve defects such as complete transposition of the great arteries or hypoplastic left heart (10). According to a study from Northern Norway, 4 out of 23 infants with SCHD died soon after birth, which represents a mortality of 17.4% (11). The prevalence is estimated to be around 4 per 1000 live births (10-12). The risk of SCHD seems to be positively related to maternal age (13)

The ultrasound screening alternatives for SCHD considered here involve nuchal translucency measurement in the first trimester. This is an indicator of serious congenital heart defects as well as Down syndrome (12), and the two conditions may sometimes be present simultaneously. However, if chromosomal anomalies are ruled out, the relevant follow-up diagnostic tests are not invasive, but simply involve referral to a specialist for a more thorough ultrasound scan. The same applies to the routine scan in the second trimester. Suspected SCHD in the second trimester can be investigated in an ultrasound scan using the so-called four-chamber view of the foetus' heart (12). Visualisation of the ventricular outflow tracts may enhance diagnostic precision (10).

Current practice

The potential number of ultrasound scans per year is determined by the number of pregnancies, which in turn may be estimated by the number of births. There is of course, some overlap here given that a pregnancy may start in a given year and end in another. In addition, it is likely that a number of early miscarriages go unrecorded. The number of voluntary abortions was 14,132 in 2006 (14), 95 % of which took place before the 12th week of gestation. The number of births in Norway has in the decade from 1996 to 2006 been approximately 58 000 per annum, as seen in figure 1 below.

Figure 1 Number of births in Norway, 1996-2006



Source: Statistics Norway, 2007

All pregnant women are offered a routine ultrasound scan between the 17th and the 19th week of gestation. This most often takes place in a hospital outpatient department, but may also be carried out in primary care. The purpose is to obtain information with regard to the foetal age to estimate the term, the foetus's anatomy and development, the number of foetuses, and the location of the placenta (15). Where an anomaly is suspected, the pregnant woman is referred to specialists for diagnostic testing at one of the major hospitals in Norway.

Current guidelines however do allow for ultrasound in the first trimester to be offered to a select group of pregnant women, but this is not considered part of the routine ultrasound programme, but rather a part of a genetic counselling and foetal diagnostics service (7;15;16). To be eligible, pregnant women have to satisfy one or more of the following criteria:

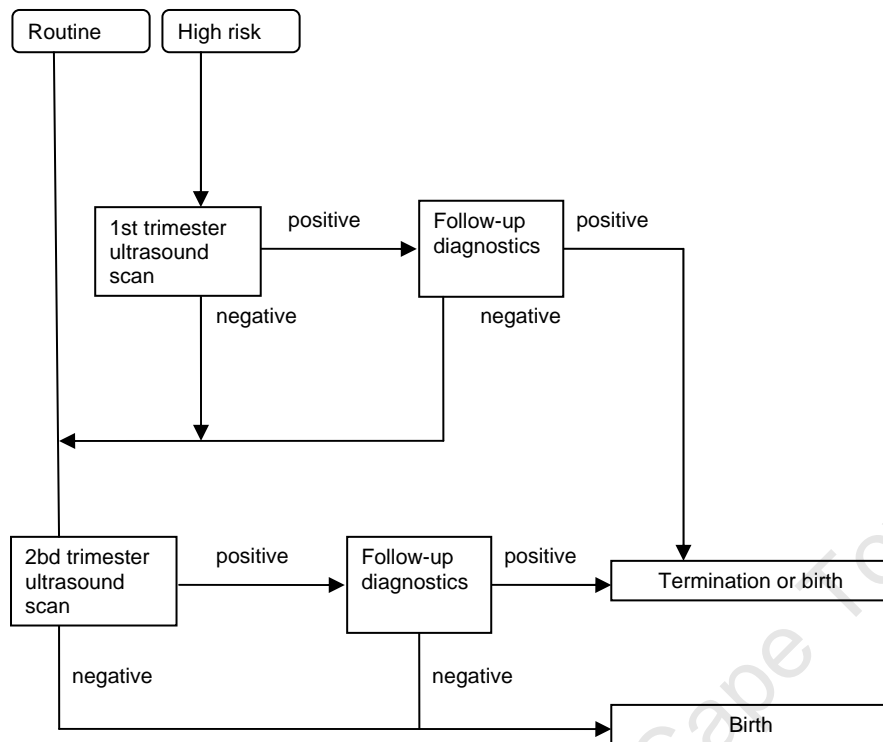
- 38 or older at the end of their term.
- Either themselves or their partner
 - have conceived a child with a serious congenital disease or anomaly (for example chromosomal disorders)
 - have a documented increased risk for serious foetal disorders
- Use medications which may harm the foetus
- Have had signs of anomalies detected through an ultrasound scan

- Who find themselves in a difficult life situation and who maintain that they will not be able to cope with the extra burden a sick or strongly handicapped child might pose.

The latest figures available as to the number of women who fall into this category are from 2000 (17) and suggest some 5 000 women per year.

According to current policy, Norwegian pregnant women are therefore allocated to one of two paths described as “Routine” or “High risk” in the flowchart below. If a strategy of universal scanning in the first trimester is implemented, all women will follow the “high risk” path. The Norwegian health authorities have only considered an extension of the screening programme to include a service of universal screening in the first trimester. The current practice of screening in the second trimester is not challenged, at least not from an official position. The strategies compared here therefore only differ in terms of the approach taken in the first trimester of pregnancy, and have been named accordingly:

Figure 2 Flowchart of the antenatal ultrasound screening process



Objectives

The primary objective of this analysis is to model the costs, outcomes (anomaly detected) and the incremental cost-effectiveness in terms of cost per additional anomaly detected of alternative screening policies, from both the health care and societal perspective. The anomalies incorporated here are Down syndrome and serious congenital heart defects.

Assuming 60,000 births annually, the three strategies under investigation are as follows:

Current: Current practice in the first trimester, i.e. ultrasound screening and follow-up diagnostic testing offered to a “high risk” group (n=5 000), but no screening in the low-risk group at this stage (n=55 000). Both groups however, go on to be screened in the second trimester.

Comprehensive: All pregnant women (n=60 000) are offered routine ultrasound screening and follow-up diagnostics in both the first and the second trimester.

Combined: As in the comprehensive strategy (n=60 000), but with the addition of two serum hormone tests combined with ultrasound screening in the first trimester, and regular routine screening in the second. The serum hormone tests, hCG and PAPP-A, are only considered as determinants of the risk of Down syndrome and will therefore not affect the performance of the test for SCHD.

The secondary objective is to assess the total costs, both direct and indirect, of all three strategies.

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2 Literature review

In the review of the literature, it seems reasonable to start by looking at the definition of screening in general and antenatal screening in particular, before moving on to examine the potential harms and benefits. Finally, a presentation is given of how screening programmes might be evaluated and of some of the challenges that arise in terms of the design and interpretation of such evaluations.

Screening: Definitions and objectives

Screening in general

Screening is, in the stripped-down definition of Merriam-Webster's medical dictionary "to test or examine for the presence of something (such as a disease)" (18). It is probably unfair to accuse a renowned medical dictionary of being too concise, but in this case such a definition would not suffice: What, for example, would be the difference between a normal medical examination in which blood pressure and urine samples are taken, and a screening programme for hypertension or proteinuria? Thankfully, the literature on screening, why it is done, to whom, by whom and not least at what time, is nothing if not extensive. There seems a general consensus however, that the objective of screening is to systematically separate those afflicted – or with a high risk of becoming afflicted – from those who are not, so that some form of health intervention targeted at the former group might be planned, and resources set aside (19). Ideally, this would take place in a situation where the screened individuals are still in a curable stage of disease (20).

For screening to make any sense, it should be performed on a relatively large scale, in a systematic fashion, and on individuals who appear to be healthy. The process is therefore often understood as a public health intervention, which suggests that it has to be a co-ordinated effort, either by government or some other sizeable organisation with the public interest in mind, serving the purpose of identifying those who already are - or those who are likely to become - sick (21). Governments may therefore initiate screening programmes and actively encourage parts of the population to enrol, and also screen selected segments of society routinely while in school or in the armed forces. The benefits of screening were first demonstrated after the Second World War, when mass miniature radiography was used to detect tuberculosis (22). The availability of relatively cheap and non-invasive screening tests

ensured that a number of mass screening programmes could be implemented in the post-war period (20). Holland & Stewart (22) report that the possible economic implications of screening were observed as early as the 1900s, when Morris Cullen, medical director of the Kaiser Programme health maintenance organisation, suggested that regular screening could reduce costs and utilisation of health services in the United States. However, the authors also refer to the popular screening programme against cervical cancer in the UK in the 1960s and 1970s, which involved a simple smear test but nevertheless placed a huge strain on cytology laboratories, as an example of a waste of public resources. That screening is often undertaken by governments does not imply that people might not on an individual basis decide to test themselves in large numbers even if there is no co-ordinated effort or encouragement from the authorities. Such behaviour, sometimes referred to as on-demand testing, is therefore not necessarily screening in the traditional sense (23). One could argue however, that if sufficient on-demand testing takes place, whether it be in a public sector health service setting, a private clinic (24) or even at home (25), this would constitute a *de facto* screening programme in the sense that it would lead to a change in demand for health treatment or prevention services that might not have occurred in the absence of mass testing. Although not a public health intervention, it might still be analysed as if it were. Not yet a common household appliance, the development in ultrasound technology has nevertheless been formidable, and obstetric ultrasound services are offered privately in a number of countries. Some are sceptical to the commercialisation of such services, on the grounds of inequality of access (26) or the lack of a cohesive system to care for those who test positive for some condition (24) or to allow for sufficient resources to be diverted to treatment. That is not to say that governments may be the more efficient provider; as Holland & Stewart (22) point out, screening may sometimes be carried out more for political – to show that the government cares – rather than for medical reasons. Moreover, mistakes are likely to be made regardless of who commissioned the screening test, as long as the test itself is imperfect.

A screening test is intended to yield either a positive or negative result, but it is the test's performance which determines the degree to which the result can be trusted. The test therefore does not offer a conclusive answer, but rather an indication of whether or not a condition is present or not. Individuals may be referred for further testing with a so-called “gold-standard” test but even such tests do not necessarily provide confirmation (21). The test performance is usually measured in terms of sensitivity and specificity. The former is a fraction denoting the number of people testing positive out of the number of people who actually have a given

condition, hence “picking out” those who are actually affected. The latter measures the number of people who test negative out of those who do not have the disease. Particularly in the case of ultrasound scanning, these indicators are products of both the technical standard of the test as well as the skill level of the ultrasound operator. Ideally both indicators should be high, to minimise the number of false positives (one minus specificity) and false negatives (one minus sensitivity). False positive cases involve unnecessary and sometimes irreversible health interventions, as well as stress and anxiety (27), whilst false negative cases mean that treatment of a condition will be delayed or not occur at all, there may also be negative psychological effects and the public confidence in the screening test may be affected negatively (28).

Antenatal screening

Antenatal or prenatal screening is simply screening that takes place at some point(s) between conception and birth. It could be argued that antenatal screening may take place even prior to conception to the extent that couples who see themselves as “high-risk” seek genetic counselling prior to deciding to have a baby (22). Ultrasound scanning is a procedure used in antenatal screening involving a non-invasive diagnostic imaging device with a so-called transducer scanner being moved either across the abdomen or through the vagina to produce radio wave images of the foetus onto a screen. The first two-dimensional ultrasound machine was built in the UK in 1956 (29). The original purpose was to determine gestational age, the location of the placenta and the presence of multiple pregnancies. As the technology developed, the scanners could also be used to spot certain antenatal anomalies. Routine scanning in the second trimester (week 18) was introduced as a health service paid for by the public purse in countries across Western Europe in the 1980s (22). Since then, some countries have extended the coverage to include a scan in the first trimester. A survey of policies with regard to routine ultrasound scanning in 18 European countries in 2004, conducted by Boyd (2), showed that 4 countries, Sweden, Denmark and England/Wales among them, had implemented a policy of two scans per pregnancy. Five countries had 3 scans, including France, Germany and even predominantly Catholic Italy. Ireland and Spain had none and so, perhaps surprisingly, did the liberally-inclined Dutch. Norway maintains a general policy of offering a free ultrasound examination to all pregnant women in the second trimester, and has done so since 1986 (30).

The perceived benefits and harms of screening

As has been noted, it is usually the case that a screening test cannot entirely rule in or rule out a condition, but merely suggest a change in likelihood of its presence. The benefits - and disadvantages or harms – associated with a screening test will thus to a great extent depend on its performance characteristics (sensitivity and specificity) but also on external factors such as the prevalence of the condition(s) in question and the treatment options available if a test is positive (22). The original purpose of ultrasound screening was to assist in determining the term date, the position of the placenta and existence of multiple pregnancies. It is hardly controversial to claim that the provision of such information to obstetricians and parents would help in the planning of the pregnancy (31) and the neonatal period, especially if a difficult delivery is anticipated. Today however, the information provided by ultrasound scanning may be used for more advanced purposes, namely as visual assistance in operations upon a foetus before birth. The first such procedure was carried out in 1982 for obstructive uropathy. Although the operation was technically a success, the patient unfortunately died after birth due to other conditions (32). Improved ultrasound technology, along with the advance of antenatal surgery techniques, have brought about rapid advances in the field of foetal medicine, and the option of *in vitro* treatment for some conditions prior to birth (3). The last two decades have, according to Kumar & O'Brien (32), seen antenatal surgical interventions for conditions besides obstructive uropathy such as spina bifida, congenital diaphragmatic hernia and cystic adenomatoid. The procedures do not necessarily have to take place prior to birth: Andrews *et al.* (33) refer to a condition in which antenatal diagnosis is deemed particularly important with regard to the planning of the birth and complicated neonatal reconstructive surgery; hypoplastic left heart syndrome. Ultrasound scanning may hence lead to an improved prognosis for some foetuses since they may receive treatment sooner rather than later, and the treatment may be of a less radical kind than would otherwise have been required (34). On the other hand, considering the worst case scenario of a lethal malformation being found in the foetus, a missing brain for example, ultrasound offers the chance to terminate the pregnancy sooner rather than the mother having to proceed to give birth to a stillborn child. If a non-lethal but serious malformation is found, late abortion may be an option, but there is also an opportunity given to prepare for a challenging but potentially rewarding life with a strongly handicapped child.

A negative test will in most cases provide reassurance to parents. The flipside of the coin is the fact that, due to the fallibility of the test, there is a risk of the test result being wrong, i.e. rendering a false negative case. The need for reassurance is after all, the prime reason why women with normal risk profiles desire ultrasound testing, or at least this is the case in Denmark, given the conclusions of a survey of 370 pregnant women from that country published in 2006 (35). It also seems that the desire for a picture of the baby is a factor, especially among women pregnant for the first time and those from lower income groups. However, there might still be some degree of stress and anxiety related to the perceived lack of safety of the scan itself (36). Although it has been suggested that exposure to diagnostic ultrasound during pregnancy may be associated with reduced birth weight and childhood malignancies or neurological disorders, no evidence of this has been found. The evidence is somewhat stronger with regard to the proposed link between antenatal ultrasound exposure and left-handedness (36). It is hardly the prospect of a left-handed child however, that is the source of the anxiety involved in the screening process, but rather the fear of a lethal or serious anomaly. This may arise before the screening takes place, at the screening test and at follow-up tests, and may even be experienced by people other than the person being screened (34;37). As Karnon (37) notes, the introduction of a universal first trimester ultrasound scan may lead to a growth in unnecessary anxiety, simply because foetuses with serious defects which would otherwise have led to a miscarriage will now be detected, and an active decision to terminate the pregnancy may have to be made. However, the fact that screening permits such decisions to be made might, according to Mooney & Lange(38), mean that older women who might have thought twice about screening in the absence of screening would now consider conceiving, prompting the birth rate to go up. This postulation has not been substantiated, nor is it as yet possible to find evidence to support the notion that termination rates (out of the total number of pregnancies) would rise as a consequence of introducing an additional ultrasound scan (2).

There are no inherent health benefits associated with the screening process itself (39), however, irrespective of the outcome, parents' access to screening facilities may give rise to feelings of empowerment and control (37), the main short-term benefit constitutes information. In the longer term, the provision of such information may or may not lead to health interventions being carried out. In most postnatal screening processes, this means that diseases may be treated and lives may be saved. As mentioned, such interventions do indeed play a role in antenatal screening as well, given that some conditions may be treated prior to

or immediately after birth,. This would however, only mean that screening has any value if it yields certain outcomes. The isolated value of the screening process is rather, according to Cairns (40), derived from the information it provides which should form the basis of decisions that in some way are different – presumably better - from those that would have been made in the absence of this information. Cairns is nevertheless quick to point out that value may not necessarily depend on the decisions made on the basis of screening information, but merely on the supply of the information itself. In other words, a screening test may be of value even if its results do not have any bearing on prognosis or any subsequent intervention (34).

Berwick and Weinstein (41) for example, found that a quarter of the value gained by pregnant women from routine ultrasound screening was not related to any decision, just information for its own sake. Lange *et al.* (42) also found that information from screening – in their case for carrier status for autosomal dominant polycystic kidney disease (ADPKD) – was valued even among women who expressed no intention to abort even if they tested positive.

Economic evaluation of antenatal screening

Whether co-ordinated or not, screening is a health intervention, and as any other health intervention it involves benefits and costs. Any intervention involving benefits or costs may be subjected to economic evaluation, and screening argues Donaldson (43), is no exception. In the case of antenatal screening, one might expect such a position to be - at least mildly – controversial. After all, as revealed in Reynolds' (44) study on British research ethics committees' attitude towards screening, the debate regarding if and when antenatal screening is justifiable has by no means been laid to rest. There seems however, to be little debate as to whether the benefits and costs of screening should be made explicit. The discussion among health economists tends rather to centre on *how* it is to be done. Perhaps this is to be expected, since people who are against screening are likely to base their argument on ethics, thus rendering the economics irrelevant. Those who are in favour of evaluation, will have moved on from the question of whether screening can be justified on economic grounds to one of “by means of which methods can it be carried out?”. Although there now exist well-defined criteria that stipulate when screening may be carried out and how the results are to be presented, as for example those laid down by the UK National Screening Committee (19), . there are no formal guidelines pertaining to the economic assessment of such activities (34). There has been a great deal of discussion among health economists regarding methodological issues in the economic evaluation of antenatal screening, particularly regarding the choice of

outcome and hence what type of economic analysis is most appropriate. The arguments relating to these issues are summarised below, and although the main focus is on the outcomes - or benefits - side of the equation, the economic analysis of antenatal screening poses challenges related to cost calculation which are also accounted for.

Outcomes: Cost-benefit analyses

Screening is evidently more complex to evaluate than other health interventions as it has a wider range of both positive and negative outcomes. Furthermore, it may involve investments in both information and – indirectly – in long term health status (39;43). The multifaceted characteristics involved, says Donaldson (43), have bearings with regard to the manner in which screening is dealt with in an economic evaluation. Several authors (34;40;43;45) consider the results of screening tests as a hierarchy of outcomes. In such a structure, the number of cases of a given malformation detected for example, would be considered only an intermediate outcome whereas a higher-order or final outcome would be the total value of the screening process to either a group targeted for screening or society at large. The most appropriate way to assess such interventions, according to these authors, would be to conduct a cost-benefit analysis, as this type of analysis is better than a cost-effectiveness analysis at capturing final outcomes – or in Donaldson's (43) words "the ultimate objective". In cost-benefit analyses, the objective is to compare discounted future streams of benefits, measured in pecuniary terms, and costs in order to measure the net benefits associated with a project (46). Hence, the merits of a project or programme can be calculated in absolute as well as in relative terms (46): Is it worthwhile to screen at all, and if so, which method of screening should be chosen?

However, how does one measure the benefits of screening in money terms? The willingness-to-pay - or contingent valuation – method, involves asking people how much they would be willing to pay for a proposed health intervention (43;47). In principle, the method should reflect the total value placed by an individual on the benefits perceived to accrue from the intervention. A few studies of this sort have been published in the field of antenatal screening. For example, one by Berwick and Weinstein (41) which revealed that 44 % of the value attributed to screening by women with normal pregnancies was related to information which had no medical significance. Another, by Caughey *et al.* (48) from California, showed that willingness-to-pay tended to vary with maternal risk and income levels. The method was

also used with regard to cystic fibrosis screening (49) where women were asked to state their willingness-to-pay before and after the test. The results indicated that those women who tested negative were willing to pay 16% more for the result than their stated pre-test willingness to pay. Theoretically tempting as the method may be, it involves a number of caveats, apart from the issue of the timing of the question. Donaldson (49) has argued that the further away one moves from a concrete measure such as the number of detected cases towards some general measure of wellbeing, the harder it gets to measure. Moreover, the researcher has to decide whom to ask (likely candidates for the intervention or a sample of the general population). Some people may consider the concept rather alien, either because they are not used to being charged for health services (4), as would be the case in Norway, or because they are reluctant to place monetary values on life and suffering (34).

Outcomes: Costs averted

Not everyone is averse to placing a monetary value on life and suffering, indeed that is what health economists do. So-called cost of illness studies abound in the health economic literature. These studies assess the direct and indirect costs that arise due to a disease or condition, whether it be predominantly congenital such as multiple sclerosis (50), or lifestyle-related such as obesity (51). The purpose of studies like these is to demonstrate the economic benefit of reducing or removing the disease (52). Therefore, they are likely to be useful in planning health care spending (53) and making priorities regarding research (52). The latter may be the reason why organisations for handicapped people sponsor cost-of-illness studies, although one could imagine that some of their members could feel stigmatised upon being told that their cost of illness, or economic burden of disease, is quite substantial.

One should hence not be surprised upon learning that health economists also place a value upon the illnesses and conditions sometimes referred to as anomalies, birth defects or malformations, which are investigated during antenatal screening. The objective is rather different in the context of antenatal screening however, as the discovery of an anomaly may well lead to its removal, and disregarding foetal medicine for a moment, this is impossible without also removing the potential life to which it is attached.

The notion of placing a value on a life – or rather the removal of such – becomes particularly visible in economic evaluations of screening interventions in which resources saved, or “costs

averted”, as a result of discovering and then aborting an affected foetus are included. These savings are often treated as benefits in cost-benefit analyses, although they should strictly speaking, according to Shackley (47), be treated as costs. Indeed they often are in cost-effectiveness analyses, as discussed later. The earliest economic evaluation of screening for Downs syndrome, a cost-benefit study by Gill and colleagues from 1987 (54), was according to Karnon (37) of the “costs averted” type. In this study, the difference between the lifetime costs of taking care of a child with Downs and a “normal” child are calculated, multiplied by the number of detected cases and incorporated as a benefit. Another study, by Cusick (55) employs the same technique, although the net cost of a Downs child seems somewhat arbitrarily set at 500 000 US dollars.

The majority of “costs averted” studies are concerned with Downs, although studies incorporating the lifetime costs of spina bifida (56;57) as well as other anomalies such as major cardiac disease, cleft lip or palate, renal agenesis or dysgenesis, urinary obstruction, lower or upper limb reduction, omphalocele, gastroschisis, and diaphragmatic hernia have been published (57). In addition, Karnon *et al.* have calculated lifetime treatment costs of beta-thalassemia (58) and sickle cell disorders (59) and suggested that they be used in screening evaluations. Brown and Buxton (34) note that some authors may have qualms about such studies and therefore do not incorporate any benefit measurement beyond the number of cases detected. They maintain however, that the omission of what they call the “true effect”, i.e. the costs averted, involves a failure in addressing the full resource implications of initiating a screening programme. It should be pointed out that they also emphasise the costs that may be saved as a result of improving the prognosis of a foetus which is not removed. One could argue that the costs averted approach should not be seen as being any more incorrect from an economic standpoint than one involving a cost of illness. One could further argue that an anticipation of the economic burden associated with extra care is a real factor in determining people’s decisions to screen, especially in countries with a low level of public health care provision.

Other authors are less positive, and have criticised the studies of the “cost averted” type for the implied assumption that there are no net benefits from a true positive result (38;43;60) and for not considering the fact that parents might not choose to terminate. The value of the un-terminated life is not calculated but for the economic burden it imposes on society (61). Anxiety and reassurance related to screening are seldom seen to attract attention (4), nor do

the studies, in Macones' view (60), account for "collateral damage" – the loss of a foetus as a result of CVS or amniocentesis, which – if a consistent logic were to be followed – would incur a lifetime's productivity loss. The inclusion of the costs and benefits that are to be added tends to be a normative affair, argues Cairns *et al.* (40) referring to the practice of adding the costs of lost output for a life with Downs syndrome, adding drily that: "For most parents, children yield benefits exclusive of their contribution to output." (Cairns *et al.*, 1992, p. 109) As Alderson puts it, these studies miss out on the huge variation in severity and functional capacity of children with Down syndrome, and what kind of life children with Down syndrome get to lead. However, the essential point made by Cairns *et al.* is that there are no objective outcomes in the area of antenatal screening. Or as Donaldson (43) puts it, the benefit measure depends on the question the analyst is seeking to answer.

Cost-utility analyses

Might then cost-utility analysis be a more appropriate tool with regard to the evaluation of antenatal screening? This type of analysis involves an outcome measure which takes into account of the quality of health states experienced over time, expressed for example in the quality-adjusted life year (QALY) in which health states are assigned a utility weight from 0 (dead) to 1 (perfect health) (46). While retaining the feature of a generic outcome unit that facilitates comparison across different types of interventions (34), it avoids the potential controversies associated with valuing the results in pecuniary terms. Despite this, there are very few cost-utility studies of antenatal screening. One study of this variety was published in Norway in 2007; Killie *et al.* (62) measured the number of quality-adjusted life years accruing to pregnant women screened for neonatal alloimmune thrombocytopenia. The quality of life measures however, appear to relate to the children that may be treated for this particular disease after birth, and not to the utility or disutility generated by the antenatal screening programme to the parents prior to birth. Harris (63) too looks at isolated parts of the screening process in his 2004 cost-utility study of screening for Down syndrome with and without invasive testing (amniocentesis and CVS), but the design of the study was seemingly aimed at isolating the effects of diagnostic testing. This segmentation is perhaps due to the potential for changed utilities over time. On the one hand it appears to be difficult to design a study that measures utilities in relation to an exhaustive screening programme given that one would either have to question women over several points in time or ex post. On the other hand some authors (34) argue that the measurement instruments for utility may not be sensitive enough to

capture the disutility related to transient screening-related anxiety which will hence not appear in the cost-utility estimations. Petrou (64) notes that preferences for certain health states may differ depending on whether or not the pregnant woman has experienced them and points out that parents may adjust well to bringing up a child with Down syndrome. Mooney and Lange (38) are also concerned with preferences and information, but this time with respect to the doctor-patient agency relationship and thus whose preferences enter the equation; the obstetrician's, the midwife's or the pregnant woman's. There may be a host of reasons for the small number of cost-utility studies in this area. Eliciting utilities is a time-consuming process. Moreover, even though money is no longer the outcome, one hasn't entirely left the ethical minefield since some maintain that it is not only the preferences of pregnant women that may be measured, but also for example those of the public at large or people with Down syndrome or some other condition for which there is a screening test.

Cost-effectiveness analyses

Cost-effectiveness studies measure outcomes in terms of natural units such as life years gained or strokes avoided and are particularly suited for cases where a specific outcome is to be maximized under a given budget (46), assuming that at least one of the alternatives is worthwhile. The focus is hence on relative efficiency, and the main advantage of the method is its simplicity: This type of evaluation however, only permits one type of natural unit to be compared at a time. Cost-effectiveness analyses therefore miss out on the broader benefits of ultrasound. Since the outcome selected most often is related to the search for and discovery of an anomaly, the outcome does not capture other benefits of screening including the value of reassurance, information and so on. These items are in a sense intangible, and may be left out precisely because they are so difficult to integrate consistently in an analysis. That is not to say that all cost-effectiveness studies of antenatal screening relate to anomalies for which nothing can be done: For example, a study from Finland from 1996 (65) based on a randomised clinical trial of 9 310 women compared the effect of one-stage ultrasound to no ultrasound on perinatal mortality and found a cost per perinatal death avoided of USD 21 938 (1996-prices).

As mentioned previously, the analysis should be geared to the question one wishes to answer. Therefore, in moving from the domain of allocative efficiency (cost benefit or cost utility analysis) to that of technical efficiency, in other words from whether to screen to when and

how often, cost-effectiveness analysis may be the most appropriate method (34;47). It is however, important that the evaluation should capture the essence of the programme investigated. The number or proportion of cases detected with a given condition has been used as an outcome measure in economic evaluations of antenatal screening (34), in which results are expressed as costs per (additional) case detected. For some, such a measure is arbitrary and doesn't carry any inherent value. Sassi (45), for example, believes the measure is a "shortcut". However, repackaging, as it were, the measure in the phrase "reproductive choice over the outcome of an affected pregnancy" seems more constructive and easier to grasp (34;66). Though "affected pregnancy" might mask a wide variety of conditions, since an ultrasound scan can indicate the presence of more than one disease, it makes decision-making more complex (39). Would it be fair for instance, to lump anomalies of different degrees of seriousness together into one generic "detected case" measure? One solution to this challenge is to categorise conditions into a few broad groups, as was done by Bricker *et al.* in the UK (67). This leaves the question of how much the discovery of an additional "affected pregnancy" is worth, or in other words; what constitutes a reasonable threshold within which the incremental cost effectiveness ratio has to lie (34)?

Some cost-effectiveness studies go further than measuring cost per detected case. Ritchie (68), for example, includes the cost of terminating an affected pregnancy, and is in this regard not quite aligned with the "reproductive choice" notion. Odibo *et al.* {Odibo, 2005 10 /id}, although they stop short of calculating extra costs to the life of a child with Downs syndrome, do record the number of live born babies with the condition as an outcome as well as the number of detected cases. This assumes some decision as to whether or not to terminate has been taken regarding the foetuses with positive tests. Harris (69) too adopts the same procedure. Other studies, such as Cusick *et al.* {Cusick, 2003 477 /id}, and Vanara *et al.* 2004 (70) go further, and may be seen as being in the same vein as the "cost averted" studies discussed earlier. However, as opposed to the "cost averted" studies, these evaluations handle the cost of care for children with anomalies on the cost side of the fraction, rather than on the benefit side.

Cost issues

As we have seen, much of the debate on economic evaluation of antenatal screening tends to centre on what the benefits are, and how they are to be measured. We have briefly touched

upon some cost issues with regard to what items to include, or in other words, when to stop including them. However, there are further costs issues, perhaps more technical in nature compared to those associated with the benefits, but which may nevertheless lead to significant variation in results, and which therefore render interpretation and comparison of results in this field difficult. Problems associated with the cost side of the fraction might be how to address shared resources, for instance among different diagnostic procedures and tariffs which do not necessarily reflect the opportunity cost of scanning or diagnostic services (45). An expansion of a screening programme may, rather than a replication of entire facilities, involve reorganisation and efficiency gains which are not reflected in costs if they are measured by proxies such as tariffs. Brown & Buxton (34) cite an example of a small increase in screening which will involve incremental costs lower than current average costs, since the latter already embody costs of investments in specialist equipment. Because of differences in capacity and potential economies of scale, screening costs may well differ significantly across contexts.

Realistic costing studies which document actual resource use are therefore warranted. An example of a rather thorough costing study which attempted to measure the "real" costs of ultrasound scans was Henderson *et al.*, which utilised top-down and bottom-up methods to elicit the cost to the NHS, pregnant women and their employers of ultrasound scans at Liverpool Women's Hospital in 1998 and 1999. The study concluded that routine scans cost in the area of GBP 14-16 per scan. Follow-up procedures were significantly more expensive. The opportunity cost of time to the women and their employers were estimated to lie in the region between GBP 9 and 15. Costs proved to be lower than what was found in the literature at the time, and were also used as input data in the evaluation by Bricker *et al.* (67). Bricker *et al.* stressed that indirect costs are important, but it could be argued that their method of measurement was somehow inequitable: The time of women going for a scan while at work was measured using the hourly wage rate GBP 5-37 net of taxes and social security contributions. Meanwhile, the time of employed women who were on holiday while the examination was carried out was valued at 40 % of the working women's time, GBP 2.15. The authors acknowledge that the valuation of leisure time was to some degree arbitrary, but state that the measure was used in a sensitivity analysis. What seems rather peculiar, however, is that they value the time of unemployed women – who are assigned an opportunity cost of time corresponding to that of cleaning work or informal care, GBP 4. An unemployed woman going for an ultrasound scan thus brings about a higher cost to society than an employed woman taking time off from her vacation, which seems somewhat incoherent.

As with other types of technology, the more advanced the machine, the more expensive it is likely to be, a feature which was duly noted by Hagenfeldt *et al.*, who in their 1998 evaluation of routine antenatal ultrasound screening in Sweden divided the scanners into three technology classes. A simple scanning technology class with 2-dimensional and simple 3-dimensional machines with a purchase price of up to SEK 400 000, a medium class with colour flow and spectral doppler which could be used to measure fluids (up to SEK 800 000) and a top class, incorporating technology of similar features as the medium class, but more advanced in terms of diagnostic precision, at a cost of up to SEK 1 200 000. The machines in the top tier were thus 3 times more expensive than those in the bottom. The rapid technological advances seen in ultrasound technology pose many challenges. Not only do the costs of the machines vary, but another implication is that results of studies using different technologies are not readily comparable. The technology itself however, is only half the story. As Tegnander (71) points out, the skill of the operator with regard to the interpretation of a fuzzy screen image also plays a significant role in determining test performance.

It is therefore not surprising that reviews of costing studies and economic evaluations of ultrasound screening show a large variation in the cost per scan (67;72;73). Roberts *et al.*, for example, found the cost of a routine scan to range from GBP 18 to GBP 204. Given the circumstances, it would have been helpful to have had access to Norwegian economic evaluations with which to compare our results. Unfortunately, we were not able to find any recent economic evaluations, nor any costing studies from Norway. The closest we came was a study by Backe and Buhaug from 1994 (74) and one even older by Bakketeig and colleagues (75). The study estimated the societal costs of antenatal and obstetric care for 1908 women in a Norwegian county over 12 months. However, the data were from 1988-89, meaning that they are now 20 years old. Moreover, the cost of ultrasound was lumped together with that of outpatient visits, and together these accounted for 4% of the estimated mean cost per woman of NOK 36 300. The cost of antenatal screening was hence not very large in comparison with the total costs of pregnancy and childbirth. The largest components were those of delivery in hospital (36%) and indirect costs related to work absence (43%). The study by Bakketeig *et al.* was based on a randomised trial comparing ultrasound in either the 19th or 32nd week of gestation to routine antenatal care at a time when a second trimester scan was not common practice. They found an average extra cost per pregnancy of USD 250 among those screened, due to increased number of hospital visits. Both these costing studies

probably provided relevant costing information at the time of publication, but due to the rapid change in the design and use of ultrasound technology, there is clearly a need for more updated costing studies in Norway. To be useful in an economic evaluation covering Norway as a whole, such studies should encompass costs from several facilities, taking into account the differences in facility size and utilisation rate.

Expansion of screening programme

Evaluation of an expansion of screening to include the combined results of first and second semester ultrasound scans is slightly more complex than measuring the effects of an intervention in separate trimesters and compare them to each other. This is because a combined detection rate has to be calculated, sometimes for several anomalies. As Gardner (76) points out, the assessment of a second trimester test should not be treated as if the first trimester never happened. In other words, the tests constitute an additional intervention, rather than a substitute (45). There is also the possibility that the first trimester intervention may not be an ultrasound scan, but a serum test. Odibo *et al.* (77) for example, compared altogether nine strategies, none of which incorporated a routine ultrasound scan in both trimesters, but concentrated on a combination of serum tests and ultrasound screening. On the whole, there seems to be few economic studies available in which the expansion of a screening programme to include a first trimester scan is evaluated, though we have found two studies from the UK: Bricker *et al.* (67) and Ritchie *et al.* (68). Bricker *et al.* compared eight options involving scans in all three trimesters in a decision-analytic model for England and Wales. However, they point out that the objectives of the first and third trimester scans are not primarily to discover anomalies. In the former, the so-called “booking scan” performed at 12-14 weeks, the aim is to determine gestational age, foetal viability, and whether there are multiple pregnancies. Some types of malformations may nevertheless be discovered. The latter scan aims to discover the position of the placenta, if there are any foetal growth restrictions, or to investigate umbilical arterial flow, but here too anomalies may be detected as a “by-product”. Bricker *et al.* calculated combined sensitivities for the scans in the different strategies to determine the detection rate for two specific anomalies (Downs syndrome and spina bifida) and two groups of anomalies (congenital heart defects and lethal anomalies). They found that the test performance varied for different types of anomaly across trimesters. The second trimester anomaly scan alone was deemed to be the most appropriate reference case given that it was cheap but still detected a large number of anomaly cases. The first trimester scan exhibited the highest average cost per case detected, but was nevertheless endorsed by the

Royal College of Obstetricians and Gynaecologists (68) along with a second trimester anomaly scan. In the Ritchie *et al.* study (68) a couple of years later covering Scotland, a first trimester nuchal translucency (NT) scan was included in the six strategies compared, whilst the third trimester scans were ignored. Serum tests in both trimesters were also analysed. The detection rates for eight types of anomaly were examined¹. The most cost-effective option was a combination of first and second trimester scanning and first trimester serum screening for chromosomal anomalies. The difference in conclusions between the two studies from neighbouring regions only a couple of years apart demonstrate the significance of the rapid development in antenatal ultrasound technology.

Conclusion

Antenatal screening has a lot in common with regular screening, but there are also clearly some differences: Antenatal screening is more multidimensional in terms of both how the tests are carried out and what they might reveal (39). The consequences of antenatal screening may in some cases also appear more dramatic than most other screening processes, even screening for potentially lethal diseases such as cancer or AIDS. It is therefore reasonable to expect that the economic evaluation of antenatal screening is somewhat more complex than the evaluation of other screening processes. Although, to cite Nilsson *et al.* (73), the availability of economic evaluations of antenatal screening may be relatively good this does not necessarily imply that the evidence base supporting a particular policy is wide. Transferring results from one context to another may be challenging and even inappropriate. The incidence and prevalence of the screened condition(s) may be different across geographical areas (34), as may be the relative prices and organisation of care (73). The type of technology and skills of the operators is also likely to vary, and is inextricably linked to the time at which the study was carried out. Hence, the gestational age at which the scans are performed is only one factor that may serve to explain the variation in costs and effectiveness in screening programme evaluations. The capacity level, technological standard, operator skills and costing methods are others, which mean that the comparison of studies across geographical contexts and time should be undertaken with caution.

¹ Anencephaly, spina bifida, cardiac defects, renal tract defects, abdominal wall defects and congenital diaphragmatic hernia

As screening interventions became widely employed, there has also been a development of standardised guidelines as to when a screening procedure is appropriate, and how the performance of the screening tests is to be evaluated. One example is the guidelines formulated and updated by the National Screening Committee in the UK (19). No such consensus has hitherto been established for the conduct of *economic* evaluation of screening programmes, however. Petrou (78;79) and Sassi (45) argue that many evaluations of antenatal screening are of poor methodological quality, particularly with respect to capturing the full range of costs and benefits. However, such an objective may be considered somewhat ambitious as long as there is no established consensus as to what, precisely, the full range of costs and benefits constitutes.

University Of Cape Town

3 Methods

Type of analysis

The objective of this study is to assess the costs and consequences of an extension of the Current ultrasound screening programme to incorporate universal testing in the first trimester, with or without the use of serum hormone tests. As noted in the preceding chapter (literature review), the choice of outcome measures in a study such as this is not obvious. However, since one may have qualms about the pricing of a life avoided method, a cost-benefit analysis is considered unfavourable in this context. There do not seem to be any Norwegian quality of life surveys available that could be used in a cost-utility analysis. Following the example of Bricker *et al* (67), it seems reasonable to restrict the analysis to a cost-effectiveness analysis, estimating the number of detected cases of both Down syndrome (DS) and serious congenital heart defects (SCHD). Costs are recorded up to the point at which a potential follow-up diagnosis either confirms or rejects the presence of an antenatal anomaly. Whatever happens thereafter is beyond the scope of this analysis. The results will be expressed as the incremental cost per extra anomaly detected, which is the incremental cost effectiveness ratio (ICER) of a programme extension relative to Current practice. The costing is carried out from the perspective of a third-party payer. Indirect costs are accounted for in the form of lost productivity, but travelling costs are not included.

A simple decision-tree model has been developed using TreeAge™ (80), in which three strategies are compared (see below), on the basis of published effectiveness data from Scandinavian and Norwegian prevalence and cost sources. The model follows a cohort of 60 000 women (i.e the approximate number falling pregnant in Norway annually) through their first and second trimester of pregnancy. The strategies compared are referred to as Current, Comprehensive and Combined, as detailed in the Introduction chapter.

Effectiveness data

Effectiveness data have been derived from a review of systematic reviews of antenatal ultrasound screening conducted by Reinart *et al* (15). The review suggested that it is difficult to compare results across studies characterised by different criteria with regard to defining the high risk group, differing mean population age and often small population size. Furthermore, reported results are likely to change over time as both the equipment and the training of

technicians and midwives improves. The most recent review covered in Reinar *et al* was Nilsson *et al* (73), a report from the Swedish Agency for Health Technology Assessment (SBU). The randomised trials and observational studies employed as effectiveness data here are primarily drawn from Nilsson *et al*. However, only a few of the studies summarised in that study provide useful input data for the purposes of the analysis. An attempt has been made to select studies based on the following criteria:

- The population should to the greatest extent possible match the Norwegian pregnancy age-distribution, so as to reflect its risk profile.
- The study should be as up to date as possible in order to incorporate the contemporary standard of technology and skills of the operators. The cut-off year was 1998, as defined by Nilsson *et al*. (73), from which the studies are drawn.

There are some challenges in employing effectiveness studies that focus on one anomaly at one point in time. First of all, in practice, ultrasound screening involves a process of examination that can identify more than one anomaly. The costs of the scan are hence shared and independent of how many cases of each anomaly is detected. The cost of follow-up diagnostics however is not, and is determined by a two-stage process: First, the likelihood of testing positive for one or the other of the anomalies is determined by combining sensitivity, specificity and prevalence data from the studies. Second, the individual share of positive tests of each anomaly is calculated out of the total testing positive. This enables the results to be expressed as a single measure of effectiveness (the sum of detected cases of each anomaly)) and cost and also to be broken down by anomaly. The study data however, are drawn from populations that are not necessarily identical in terms of age and risk distribution. The second challenge relates to the fact that the effectiveness data from the second trimester is independent from that of the first. Rather than measure the effect of two scans on one population, the second trimester data results are from an unselected population with no prior risk stratification. This has been handled by reducing the prevalence rates of the two anomalies in the second trimester part of the model by removing the detected cases and confirmed negatives in the first trimester from the model population destined to be scanned in the second trimester. If this were not done, it would have been the same as assuming that there had been no tests at all prior to the second trimester, and one could have risked that the sum of the cases detected in both trimesters would have exceeded the prevalence.

Down syndrome

Nilsson *et al* (73) found 22 studies from the period 1998-2005. In terms of population, one of the studies was high risk, one low-risk, seven not given and the remaining 13 were unselected. The study by Prefumo *et al.* (81) from the UK on a selected high-risk population of 510 women scanned in the first trimester with NT was used for the sensitivity and specificity variables in the high-risk group in the Current strategy, but the standard Norwegian Down syndrome prevalence rate of 2.0 per 1000 was retained. This seems like a useful method, given that Greenhalgh (21) has pointed out that sensitivity and specificity are not affected by prevalence, but the positive predictive value, i.e. the probability of having a condition after having tested positive for it. The data for the first trimester in the Comprehensive strategy and the second trimester in all strategies were taken from Saltvedt from 2005 (82), a Swedish randomised controlled trial in which a total of 39 572 pregnant women were either scanned at 12-14 weeks of gestation, including NT screening, or at 15-20 weeks, with screening based on maternal age. First trimester data for the Combined strategy were drawn from Wald *et al.* from 2003 (83), also known as the SURUSS study. This was a prospective study which took place at 25 centres – one in Austria, the rest in the UK, at which 47 053 pregnant women were screened with ultrasound plus NT and serum tested in the first trimester.

Table 1 Effectiveness data: Down syndrome

Trimester	Strategy	Study	Sensitivity	Specificity
1st trimester	Current (high risk)	Prefumo <i>et al.</i> 2006	0.87	0.503
	Comprehensive and Current (low risk)	Saltvedt <i>et al.</i> 2006	0.76	0.962
	Combined	Wajd <i>et al.</i> 2003	0.85	0.939
2nd trimester	All	Saltvedt <i>et al.</i> 2006	0.61	0.817

Serious congenital heart defects

Nilsson *et al* (73) identified 15 effectiveness studies of SCHD, of which 9 had an unselected population, 2 low risk and the remainder unclear. As in the case of Down syndrome, there were no specific high-risk studies available in the case of SCHD, therefore the same method of using the standard prevalence in the high-risk group in the Current strategy was applied. Data from Westin (84), a study from Sweden from 2006, was chosen as the source of first trimester data for all three strategies. The randomised controlled trial featured 39 572 pregnant women who were scanned at hospitals (with NT in the first trimester) to check for

SCHD at either 12 and 18 weeks of gestation. The first trimester sensitivity was relatively low at 10%, which could be due to the difficulty of detecting malformations in the relatively small foetal heart at 12 weeks. The second trimester data were taken from a Norwegian study by Tegnander from 2006 (1), in which 42 381 fetuses were investigated for serious congenital heart defects in the second trimester. The specificity in this study was 1, meaning that all negative cases were confirmed as such.

Table 2 Effectiveness data: Serious congenital heart defects

Trimester	Strategy	Study	Sensitivity	Specificity
1st trimester	All	Westin 2006	0.1	0.992
2nd trimester	All	Tegnander 2006	0.41	1

Probabilities

The data summarised in Nilsson *et al* (73) include sensitivity and specificity, from which one may calculate some of the other probabilities required in the decision model: the risk of testing positive and the subsequent risk of being confirmed positive, which are used to calculate the number of detected cases.

The positive test rate ptr denotes the chance of testing positive in either trimester, whether it be for Down syndrome or serious congenital heart defects, and may be calculated on the basis of the following formula, in which:

sens=sensitivity

spec=specificity

(1-spec)=false positive rate

n=population

prev=prevalence

$$ptr = \frac{(sens \times prev \times n) + (1 - spec) \times (n - (prev \times n))}{n}$$

Since the model requires the calculation of the share of patients testing positive for *either* Downs or SCHD, the ptr has to be calculated on a group level, in which the parameters of the individual studies are combined.

$$ptr_G = ptr_{DS} + ptr_{SCHD}$$

The risk of being confirmed positive will depend on how many of those who test positive choose to receive follow-up diagnostics (discussed below) and of these, how many will actually turn out to have the condition, which is the positive predictive value, ppv .

The ppv for Downs, for instance, can be defined as:

$$ppv_{DS} = \frac{sens_{DS}}{ptr_{DS}}$$

As opposed to the ptr , the ppv at the group level is not the sum of the ptr of the subgroups, but can be expressed as a fraction with the sum of the detection rates of both anomalies in the numerator and the sum of the positive test rates in the denominator. The detection rate denotes the reate of detected true positive cases to the number of cases tested.

Detection rate, Down syndrome

$$dr_{DS} = ppv_{DS} \times ptr_{DS}$$

Positive predictive value (grouped):

$$ppv_G = \frac{dr_{DS} + dr_{SCHD}}{ptr_{DS} + ptr_{SCHD}}$$

Costs

Direct costs

Unfortunately, it has not been possible to find any costing study of the type conducted in Liverpool in 2001 (85) which could provide an idea of the real cost of performing an ultrasound scan or a antenatal diagnostic procedure. Even if one were available, hospitals which offer ultrasound scans in Norway tend to vary significantly in size and in regard to the population density of the area they serve. Moreover, ultrasound scans are also offered by general practitioners (GPs). There would thus be some uncertainty as to whether the costing figures would be representative on a national level. Therefore, tariffs – or rather reimbursement claims for different procedures from GPs and hospital outpatient departments to the National Insurance Administration, have been chosen to represent costs. Even though such charges are, as pointed out by Sassi (45), unlikely to reflect the opportunity costs of the procedures they represent, it may be argued that they at least represent the potential change in government expenditure in the short run. This argument is referred to in the methodological costing review conducted by Mogyorosy and Smith (86). It is not an ideal method, but for the purposes of the present study, it constitutes the only feasible solution. It is apparent however, that the tariffs do not represent opportunity costs in that they are clustered in groups. For example, the tariff for abdominal and transvaginal ultrasound and antenatal counselling are all the same. The charges or reimbursement rates associated with the procedures relevant to the model and applicable in 2006 are shown in the table below.

Table 3 Reimbursement rates antenatal screening and diagnostics

Procedure	Tariff code	Tariff, Norwegian kroner 2006
Abdominal or transvaginal ultrasound scan	B20c/B20i	219
Consultation charge	B02	127
Antenatal counselling	B20h	219
HCG/PAPP-A blood test	701h (GP)	31
Amniocentesis/CVS	B21f	389

Source: Norwegian National Insurance Administration, NAV, Outpatient Tariffs 2006, GP Tariffs 2006

Indirect costs

Indirect costs are calculated on the basis of the expected productivity loss associated with the different procedures (including travel time) and the average hourly wage rate for women in 2006 (87). The ultrasound scans are assumed to take half an hour, while follow-up diagnostics and counselling sessions are assumed to take a full hour (88). An hour is also added for travelling purposes, though the costs of travel itself is not included due to lack of reliable data. All women are assumed to work, and to return to work immediately after the consultation.

Model structure

Except for the Current strategy, in which the first node represents the chance of being scanned in the first trimester, the first node in all strategy branches determines the risk of a pregnant woman testing positive for either DS or SCHD. By structuring the decision tree in this fashion, it is possible to separate the costs for ultrasound screening and those that arise due to follow-up diagnostics. The cost of the former will be incurred whether or not a case of antenatal anomaly is actually detected. Those testing negative will proceed to the second trimester scan.

For those who test positive, the subsequent node denotes the probability of the woman proceeding to diagnostic follow-up. As pointed out in Chapter 1, such procedures are in the case of DS not risk free, and many may therefore opt not to go through with them. However, the actual proportion is not known. It may tend to vary according to age, type of test and at what time it is carried out (73;89). Intuitively, one might expect the rate to be higher in the first trimester, as the opportunity to terminate the pregnancy if any anomaly is found might be perceived as greater than would be in the second. Invasive tests, which are relevant for Down syndrome, are most likely more of a barrier than a non-invasive further ultrasound scan, which would be the option for serious congenital heart defects. A standard propensity to pursue follow-up diagnostic testing across both anomalies and trimesters has been assumed and this figure has been varied in the sensitivity analysis from 50 to 100%.

Those who test positive and who choose to proceed to follow-up diagnostics are either confirmed positive and added to the number of detected cases or confirmed negative. In either case, they are subtracted from the remaining model population so as to avoid being counted as part of the population being scanned in the second trimester.

Those who test negative on the first trimester scan will proceed to be scanned in the second trimester. As the effectiveness data for all strategies are the same for the second trimester, the only variables that will differ among the strategies here are the number of pregnant women who will be scanned in each case, as those confirmed positive have been removed from the model population and the prevalence rate at this stage. The second trimester branch structure is more or less identical to that described for the first trimester. At the triangular terminal nodes, the accumulated number of detected cases is counted for each strategy, as are the costs. A graphic representation of the decision tree is shown in the appendix. All strategies have been integrated in the same tree, but have been presented separately to make the text legible.

University Of Cape Town

4 Results

This chapter presents the results of the cost-effectiveness analysis performed using the decision analytic model which follows a cohort of 60 000 pregnant women through screening and diagnostic procedures during the first and second trimesters of pregnancy. The model's primary outcome measure is the total number of detected cases of Down syndrome and serious congenital heart defects associated with each strategy. A detected case is a result of a positive ultrasound scan and subsequent confirmation through diagnostic testing. In addition, the number of false positive cases generated by each strategy is calculated. False positive cases are defined as those who test positive in either of the two trimesters covered, but who are classified as negative at the completion of follow-up diagnostics in the second trimester. Direct costs, which are the costs borne by the publicly financed health care sector as well as by the patient in the form of co-payment, are presented along with total costs, which are the sum of direct costs plus indirect costs. These are presented separately and per detected case in the base case analysis. All costs are measured in Norwegian kroner (NOK) or in million Norwegian kroner (MNOK) in 2006 prices.

The presentation of the base case analysis includes a scrutiny of the composition of the outcomes and costs. Finally, the effect of changing the assumptions with respect to the probability that positive testing women will undergo follow-up diagnostics and the relationship between costs and tariffs is explored in the sensitivity analysis.

Base case analysis

Number of cases detected

Table 4 below shows the total number of cases detected in each strategy. In the Current strategy, a total of 468 cases of Down syndrome and serious congenital heart defects are found. The Combined strategy, which incorporates a first trimester serum test as well as ultrasound, generates the highest number of detected malformations of 625. The strategy is however, only marginally – five cases – better in terms of the objective of detecting the most cases relative to the Comprehensive strategy. The latter is identical to the Combined strategy but for the serum test. Compared to the Current strategy, which involves the public provision of ultrasound to a relatively small high-risk group of around 5 000 women, the strategies

incorporating first trimester universal ultrasound scanning enable the number of total cases detected to increase by approximately 33%.

Table 4 Number of detected cases by strategy

Strategy	Number of detected cases	Incremental number of detected cases
Current	468	
Comprehensive	620	152
Combined	625	157

The results shown above are based on the assumption of 67% diagnostic follow-up based on the experience from the Centre for Medical Genetics in Bergen (90), i.e. that two thirds of the women receiving a positive ultrasound scan will, after attending a counselling session with an obstetrician, proceed to diagnostic testing. As mentioned previously, the model only follows the cohort of pregnant women to the diagnostics stage in the second trimester, and not to the pregnancy's final outcome, whether it be delivery or abortion. Since the follow-up rate is set at a figure less than 100%, some women who test positive but who are not confirmed as such will neither be classified as a detected case nor as a false positive case. The rate is highly uncertain and has therefore been varied in the sensitivity analysis, but since the model only permits a uniform rate, this does not capture the potential differences in the uptake of follow-up testing between the two anomalies. These can be expected to differ in that the confirmation of Down syndrome involves invasive tests whereas the detection of serious congenital heart defects does not (1).

Direct, indirect and total costs

The annual direct costs associated with the Current strategy are NOK 33.2 million for 60,000 pregnancies, or NOK 664 per pregnant woman in the model cohort. The two strategies incorporating universal first trimester routine ultrasound scanning both incur additional costs in the region of NOK 33-36 million, increasing the cost per pregnant woman to almost NOK 1,400. The incremental cost associated with the Combined strategy however, is higher than the cost of the Current strategy, which is most likely due to the extra costs brought on by the serum test.

When the indirect costs are included, the costs in all three strategies are approximately doubled. Relative to the Current strategy, the costs in the two universal first trimester scanning strategies rise by more than NOK 50 million. Again, there is only a small difference between the two first trimester universal scanning strategies at NOK 9.1 million, which translates into NOK 150 per pregnant woman. As stated in the Methods chapter, the indirect costs are calculated on the basis of the hourly wage rate, assuming all pregnant women are employed and not on any form of leave at the time of the scan. This is a relatively strong assumption, which may cause the indirect costs to be overestimated. Some women may leave work only briefly for an ultrasound appointment and “catch up” once they return. On the other hand, some invasive testing procedures or prolonged counselling may require longer periods away from work (88). In addition, many women may prefer to bring their partners along for the session; these costs not been included in the model.

Table 5 Direct and total costs

Strategy	Direct costs, MNOK	Incremental direct costs, MNOK	Total costs, MNOK	Incremental total costs, MNOK
Current	33.2		68.8	
Comprehensive	66.3	33.1	122.2	53.4
Combined	69.4	36.2	131.2	62.5

Cost per case detected

A comparison of the incremental costs and incremental cases detected with reference to the Current strategy show that the Comprehensive strategy may be considered to be relatively more cost-effective than the Combined strategy, generating an incremental cost-effectiveness ratio of NOK 218 000, which is NOK 12 000 lower than the Combined strategy.

Nevertheless, implementing this strategy instead of staying with the status quo involves a doubling of direct costs whereas the number of detected cases only goes up by a third. When indirect costs are included, the incremental cost per case detected in both strategies grows to around NOK 350-400 thousand.

Table 6 Incremental costs per case detected

Strategy	Incremental direct costs, MNOK	Incremental total costs, MNOK	Incremental cases detected	Incremental direct Cost per detected case, NOK	Incremental total cost per detected case, NOK
Current					
Comprehensive	33.1	53.4	152	217 763	351 316
Combined	36.2	62.5	157	230 255	397 771

Changing the point of reference from the Current strategy to a hypothetical strategy of “No scanning”, i.e. one where no costs are incurred and no cases found, serves to demonstrate that the discovery of the additional cases in the first trimester becomes relatively more expensive in terms of the cost per case detected. The incremental costs of the strategies relative to no scanning are the same as the average costs. Detecting 468 cases in the Current strategy comes at a direct cost per case of nearly NOK 71 thousand, whereas the additional 150 or so cases detected in the two other strategies entails an average cost of around NOK 107-111 thousand per case.

Table 7 Average costs per case detected

Strategy	Direct costs, MNOK	Total costs, MNOK	Detected cases	Average direct costs per detected case, NOK	Average total cost per detected case, NOK
Current	33.2	68.8	468	70 940	146 902
Comprehensive	66.3	122.2	620	106 935	197 016
Combined	69.4	131.2	625	110 960	209 920

Interpretation of these results is not necessarily straightforward, since no decision rule as to what is and what is not cost effective can be ascertained in this context. Norway, unlike the National Institute for Clinical Excellence in the UK, does not have a semi-official threshold value concerning the willingness-to-pay for health benefits (91). Even if it did, this would be of little help as such threshold values tend to apply to benefits expressed in terms of quality-adjusted life years and not physical units such as the number of cases detected. If the objective

were to minimise the cost per detected case then retaining the Current strategy is clearly the best option. Should the goal on the other hand be to maximise the number of cases detected regardless of cost, then the Combined strategy is the most sensible choice. When compared to the Current strategy, the other two strategies involve the discovery of some 33% extra cases, but the costs rise more than proportionately. What is clear is - provided that first trimester universal ultrasound scanning is desired - the Comprehensive strategy is relatively more cost-effective than the Combined alternative. However, if the population has very high willingness to pay for finding these anomalies, the Combined alternative could be considered cost-effective.

Number of cases confirmed as false positive

The number of confirmed false positive cases derived from the Current strategy is relatively high at approximately 7 000, or 12% of the cohort of pregnant women in the model. In either of the first trimester universal scanning strategies, the figure increases by about 611 cases. This might appear somewhat odd, since one would expect the implementation of an additional scan to generate significantly more positive – and therefore necessarily false positive – cases. In practice, this is indeed true, but many of the cases in the model testing positive in the first trimester routine ultrasound scan will proceed to another scan in the second if they are not confirmed as a detected case in first trimester follow-up diagnostics. The model therefore, only counts as false positive those cases which – subsequent to the final opportunity for a diagnostic test - are classified as such. In other words, a case may be wrongfully found positive in the first trimester, but confirmed as either negative or true positive in the second and therefore not counted as false positive at the end. Based on the model estimates, the implementation of additional routine scanning and diagnostic testing in the first trimester does not contribute to a reduction in the number of false positive cases, but at least the figures are kept relatively stable. However, as a consequence of the model's assumption of 67% diagnostic follow up in the base case, as well as ignorance of “interim” false positive cases, the final number of confirmed false positive cases presented can not be used as an indicator of the number of women experiencing unnecessary anxiety. The model is not designed to estimate the number of false negatives.

Table 8 Number of false positive cases

Strategy	False positive cases	Incremental false positive cases
Current	6 972	
Comprehensive	7 583	611
Combined	7 584	612

Composition of costs and outcomes

Breakdown of the number of detected cases and confirmed false positive cases

A breakdown of the number of cases detected by anomaly is given in table 9 below.

The vast majority of the cases detected of the two anomalies covered in the model are serious congenital heart defects. These have an approximate 90% share of the cases detected in all three strategies. This is not particularly surprising, since the prevalence of serious congenital heart defects is about 20 times that of Down syndrome. The disparity with regard to the respective shares in the total number of detected cases could have been even larger if it were not for the fact that the sensitivities in the efficacy data relating to Down syndrome is on average higher than those relating to serious congenital heart disease.

The number of detected cases of Down syndrome increases by more than 100% in both the Comprehensive and Combined strategies relative to the Current strategy, but the corresponding figure for serious congenital heart defects is only 26%. The incremental number of serious congenital heart defect cases found is however, significantly larger in absolute terms. The five extra cases that separate the Combined strategy from the Comprehensive strategy are, as expected, all cases of Down syndrome, owing to the inclusion of serum tests for that condition in the former strategy.

With a Down syndrome prevalence rate of 0,002, one would expect around 120 cases of the condition to exist in a cohort of 60 000 women. The model estimates 82 cases to be detected in the Combined strategy and a few cases less in the Comprehensive strategy, which entails the detection of around 68% of all possible cases during the course of the first two trimesters, assuming a follow-up rate for diagnostic tests of 67%. As far as serious congenital heart defects are concerned, the prevalence is much higher at around 0.04, which means that the

cohort would generate some 2 400 cases. The first trimester universal scanning strategies in the model detect approximately 23% of these. In other words, provided that two out of three women proceed to diagnostic testing, two thirds of the Down syndrome cases and about a quarter of the cases of serious congenital heart defects would be discovered in the strategies which include universal first trimester scanning.

Table 9 Breakdown of the number of detected cases by strategy

Strategy	Down syndrome		Serious congenital heart defects	
	Total	Incremental	Total	Incremental
Current	38		430	
Comprehensive	77	39	543	113
Combined	82	44	543	113

As far as the false positives are concerned, most of these will be cases of suspected Down syndrome. This is primarily due to the difference in prevalence rates. Furthermore, the false positive rate for the second trimester serious congenital heart disease data used in the model is zero. As long as the specificity in the efficacy data in the model's first trimester strategies is less than 1 there will, in a strict sense, be temporary false positive cases, but many of these are picked up in the second trimester scan.

Table 10 Breakdown of the number of confirmed false positive ultrasound scan cases by strategy

Strategy	Down syndrome		Serious congenital heart defects	
	Total	Incremental	Total	Incremental
Current	6 785		187	
Comprehensive	7 367	582	216	29
Combined	7 368	583	216	29

Breakdown of costs

The structure of the costs associated with the individual strategies can be examined more closely by running the model with and without specific cost components using dummy variables. It is for example, possible to determine the proportion of each strategy that relates to the routine ultrasound scan, counselling and follow-up diagnostics, productivity loss as well as patient co-payment.

Splitting the costs between routine scanning and the services which are dependent upon a positive result, i.e. counselling and follow-up diagnostics shows that respectively 6,5%, 7,4% and 10,1% in the Current, Comprehensive and Combined strategies are related to follow-up diagnostics. In absolute terms, the follow-up costs rise by around two million Norwegian kroner following a move from the Current to the Comprehensive strategy, and a further two million if the Combined strategy were to be adopted, as shown in table 11. This is brought about by higher positive test rates in the two first trimester universal scanning strategies. The increase in costs due to additional chorionic villus sampling, amniocenteses and follow-up cardiac scans is relatively small however, compared to the cost of implementing an additional routine ultrasound scan.

Table 11 Direct costs of routine ultrasound, counselling and follow-up diagnostics

Strategy	Routine ultrasound, Direct cost MNOK	Counselling and follow-up diagnostics Direct costs MNOK
Current	31,2	2,0
Comprehensive	61,7	4,6
Combined	63,0	6,4

Costs: Patient co-payment

The direct costs presented here are mainly those borne by the health care system, though a fraction of the total expenses are billed to patients as co-payments. The patients' fees represent approximately 41% of routine ultrasound scans and follow-up diagnostic tests. The

total patient share of the Current strategy costs are NOK 13.6 million, which will increase by around 14-15 million NOK if the Comprehensive or Combined strategy were implemented. Travel costs are not included due to a lack of reliable data. Population densities tend to vary across health regions in Norway, and the cost per trip will differ depending on the mode of transport.

Table 12 Share of patient co-payment

Strategy	Total direct cost MNOK	Patient co-payment MNOK	Percent
Current	33,2	13,6	41,0
Comprehensive	66,3	27,8	41,9
Combined	69,4	28,1	40,5

Sensitivity analyses

Rate of diagnostic follow-up

A one-way sensitivity analysis where the probability of diagnostic follow-up is varied between 50% and 100% reveals that this variable has a significant impact on the average cost per detected case in all three strategies, as seen in the table below. The difference between strategies in this regard is also higher the lower the rate of follow-up diagnostics.

Table 13 Sensitivity analysis: Diagnostic follow-up rate varied between 50% and 100%

Average cost per detected case in NOK thousand by strategy

Strategy	50%	67% (base case)	75%	100%
Current	124,2	70,9	57,2	33,1
Comprehensive	168,4	106,9	89,7	57,0
Combined	175,1	111,0	93,0	59,4

If the rate of follow-up were at the maximum, all three strategies would be able to detect more than 1 000 cases of congenital anomalies. However, the absolute difference among them in terms of cases detected would not be significantly different from that generated by the base case rate of 67%. If all positive ultrasound scans were investigated further, about 94% of all Down syndrome cases could be found in the two first trimester scanning strategies, and 44% of the serious congenital heart defect cases.

Table 14 Sensitivity analysis: Diagnostic follow-up rate at 100%,
number of detected cases

Strategy	Number of detected cases	Incremental number of detected cases
Current	1 024	
Comprehensive	1 173	149
Combined	1 178	154

Relationship between costs and tariffs

The direct costs in the model are based on tariffs which – as will be discussed in the next chapter – do not necessarily reflect the opportunity cost of the activity they are intended to finance. Norway has a system of activity-based financing where tariffs are, on an overall level, meant to contribute 40% of the costs of running public health care services (92). The remainder is covered by direct transfers from the Ministry of Health. Tariffs then, are not likely to represent the full costs of health services because their production has already been subsidised. That the tariffs related to ultrasound scanning should represent 40% of the full cost is not necessarily a realistic assumption, but it may provide a better picture of the real costs than the use of tariffs alone. Therefore, due to lack of a proper costing study, we present the results in terms of average cost per case detected in the table below, with all tariffs multiplied by a factor of 2.5. As shown in the table below, the average costs per detected case rise by approximately the same factor. The costs per extra case detected relative to the Current strategy are however; significantly larger than they are in the base scenario, with ca. half a

million kroner per case associated with the Comprehensive strategy and almost a million kroner with the Combined strategy.

Table 15 Average direct costs per case detected – tariffs x 2.5 (full cost approximation)

Strategy	Direct costs, MNOK	Detected cases	Average direct costs per detected case, NOK	Incremental direct costs per detected case, NOK
Current	80,0	468	170 940	
Comprehensive	165,8	620	267 419	564 474
Combined	173,3	625	277 280	968 153

5 Discussion

Policy implications

The results in perspective

The results indicated that the number of detected cases with both the anomalies covered in the model (with an assumed two thirds of patients (67%) proceeding to diagnostic follow-up) was 468 in the Current strategy. The number increases by 152 or 157 if either the Comprehensive or Combined strategy is chosen. The sensitivity analysis showed however, that an increase in the rate of diagnostic follow-up beyond 67% could have a far greater impact in terms of increasing the number of cases detected than a change in strategy. At the same time, an increase in follow-up leads to a reduction in average cost per detected case and the number of unconfirmed false positive cases. It would therefore be reasonable for the authorities to encourage increased participation in diagnostic follow-up on efficiency grounds, rather than to implement a strategy of universal first trimester scanning. This may indeed be a sensible approach with regard to serious congenital heart defects where non-invasive tests are warranted. The caveat however, is associated with suspected cases of Down syndrome which require invasive follow-up testing. Amniocentesis and chorionic villus sampling involve a similar risk of so-called iatrogenic loss or miscarriage of 0.5-1% in addition to the background risk of 2-3% (93). This means that 1-2 fetuses will be lost for an increase in invasive follow-up testing of 3% and 10-20 would be lost if the participation rate increased to 100%. This aspect of invasive testing should be taken into account when considering the results, but is hard to quantify in economic terms. Hopefully, the need for invasive testing will be reduced with the introduction of new methods in the future. The main argument for carrying out ultrasound in the first trimester is that the detection rate for both Down syndrome and serious congenital heart defects are relatively higher than in the second trimester. With regard to the detection of these anomalies, it would make sense to move the scan if the government should decide to pay for only one ultrasound examination per pregnancy. However, there are other reasons as to why the second trimester scan ought to be retained, as it enables the detection of structural anomalies such as spina bifida.

The multidimensional aspects of antenatal ultrasound screening might be one of the factors which serve to explain why there seems to be scant evidence for the potential economic benefits of introducing universal first trimester scanning, although quite a few European countries have adopted such a strategy (2). Other factors include the lack of consensus as to how economic studies in this field are to be carried out and how their results are to be interpreted. As demonstrated by the literature review, there are few studies available that might be compared to the present study. The exceptions are Bricker (67) *et al.* from England/Wales and Ritchie *et al.*, (68) from Scotland; neither of these is however exactly the same as the model presented here in terms of scope.

As noted in the Results chapter, there is no consensus as to what constitutes an acceptable limit to the cost per case detected, neither nationally nor internationally. There is no formal requirement in the formulation of health policy in Norway, if one disregards the stipulation that pharmaceutical companies have to submit a pharmacoeconomic analysis with their reimbursement applications to the Norwegian Medicines Agency. The Rights of the Patient Act (94) from 2001 does however state that the costs of an intervention should be in “reasonable” proportion to the anticipated health benefits, although no definition of the term “reasonable” has yet been offered. Even if there were such a threshold – for example with respect to a cost per quality adjusted life year – it would intuitively seem much harder to develop a decision rule with respect to a cost per detected case. Should all anomalies be attached equal weight, for example, or should one distinguish between lethal anomalies and serious anomalies with long term morbidity as was done in Bricker *et al.*’s (67) study? One could present the results in terms of a potential increase in the probability of detection: The model shows that the overall detection rate could increase from 19% to 25% if a first trimester universal scanning policy were introduced. However, this does not circumvent the requirement of valuation of detection or its consequences, and is far more complex than for example, the assessment interventions designed to prevent road accidents or pollution.

Consequences for the health services

It is reasonable to assume that the most important questions linked to a potential expansion of routine antenatal ultrasound screening in Norway, at least from the publicly run health services’ point of view, relate to capacity. Would a move to the Comprehensive or Combined strategies, possibly involving an annual addition of some 60 000 scans and a large number of follow-up tests, require a significant increase in resources, both in terms of manpower and

equipment, allocated to such activities? Would the workload, primarily for the 463 obstetricians (95) and approximately 1 300 midwives (96) working full time in Norway in 2006 grow by such an amount that extra staff would have to be taken on? Would new scanners have to be purchased and investments in other capital equipment and administrative personnel have to be made? The answers to all these questions are probably negative. The reason for this is that there do not necessarily have to be any additional scans: The average number of scans per birth in Norway has remained at around 2 for the last 10 years prior to 2006, albeit with regional and individual variations. Backe's 1997 study (97) reported that 46% of pregnant women had met for only one ultrasound examination, but that the mean number of examinations performed per woman was 2.2. Since these figures only account for the scans administered in the public sector, the overall rate is likely to be higher in 2006 given the emergence of private providers in the interim period (88). Backe's figures suggest that the distribution of scans among pregnant women is skewed, and that a minority of women seem to undertake a high number of scans. There is unfortunately a lack of recent statistics, particularly as to the timing of the scans, but most are liable to have taken place in the second trimester. Forbes (98) found a similar pattern in New Zealand in 2004, with an average of 2.1 ultrasound scans per pregnancy, while 14% of pregnant women had none and 15,4% had more than 4 scans.

It is thus highly probable that any need for increased capacity with regard to the number of ultrasound scans has already been absorbed subject to the assumption that the average number of scans does not increase much beyond 2. There is, in the opinion of Eik-Nes (99), significant room for reorganisation in obstetric care to ensure that the number of "unnecessary" scans is minimised. There is, for example, little point in undergoing more than one scan in the same trimester if no anomaly is suspected. If this does not happen however, the number of scans would increase, but it is not possible at this point to determine whether investments would have to be made to increase capacity. If the government already funds on average two scans per pregnancy, one could question the relevance of the present analysis. However, this ignores the fact that the distribution of the scans among pregnant women and the exact timing is unknown. It may be plausible to assume that some women who test positive may decide to go for a second scan, "a second opinion" as it were, before deciding whether to proceed to follow-up diagnostic tests. The government could easily, if it were so inclined, limit the number of scans funded per pregnancy to one by means of say, a voucher

system, but this could have negative ethical implications in terms of autonomy and equity of access.

A move to routine scanning in the first trimester is nevertheless likely to have some consequences. According to Helbig (100), it may lead to extra referrals to specialist centres for foetal medicine since physicians and midwives may be uncertain as to the interpretation of the first trimester scan results. Svaasand (93) believes it will bring about different strategies with respect to diagnostic testing, with an emphasis on chorionic villus sampling rather than amniocentesis. There is however, limited evidence available on the effects on follow-up diagnostics of the extension of screening programmes. O'Connell *et al.* (101) published a review in 2006 of 11 retrospective cohort studies that examined the effect of screening on invasive testing. However, the studies were characterised as being “not high” in quality - the authors found that many of them had small sample sizes and low external validity, and none looked at changes in testing following the introduction of integrated or sequential screening methods. O'Connell observed that although there are a number of short-term studies available that evaluate screening for Down syndrome, they did not have a sufficiently long follow-up period to evaluate the long-term consequences with respect to invasive testing. However, the results from Ekelund *et al.* from Denmark (102) reveal that the extension of the screening programme in that country to one resembling the Combined strategy in the model, may actually have contributed to a significant *reduction* in the rate of follow-up testing. The Centre for Medical Genetics and Molecular Medicine at Haukeland University Hospital in Bergen, Norway (90) states in its 2005 annual report that the number of amniocenteses has gone down. The possible explanation is that the serum test which has been offered at the hospital for some time may have reduced – rather than increased – the need for invasive follow-up testing. No figures were found as to the frequency of chorionic villus sampling. A change in the form, rather than the overall volume, of invasive testing is in any event likely to have little consequence due to similar risk of miscarriage, and the cost differences are likely to be minimal. The evidence from Denmark and Bergen does however suggest that new studies on the effects of the first serum test on risk assessment and follow-up testing are warranted in Norway.

Women's preferences

One may infer from the existence of a number of private health care providers offering antenatal ultrasound scans in the first trimester in Norway, that there is indeed demand for

such services in this country. Nilsson *et al.* (73) report that women, when asked, respond that they desire screening as early as possible in pregnancy and that they feel they need sufficient time to consider their options. Studies (15;103) show that a first trimester scan does not apparently lead to any rise in anxiety compared to a second trimester scan. However, the studies reveal that the level of anxiety does increase in women who are told they have a higher risk for foetal anomalies, and that this is not necessarily reduced as a result of being confirmed false positive. Women also express concern about the risk of miscarriage in relation to invasive testing. Reinar *et al.* (15) stress the need for appropriate methods of providing information to assist pregnant women in making decisions based on risk assessment. Some women and their partners may have difficulty in grasping the meaning of nuchal translucency measurement and soft markers, and that these provide an estimate of risk rather than a definitive answer (73;104). Parents can sometimes be unprepared for adverse findings (105) and may even view the scanning session as a form of entertainment – a chance to see the child for the first time (98). Although Nilsson *et al.* (73) suggests that women considered that they were responsible for the decisions related to ultrasound scanning, Forbes (98) is highly critical of what she considers to be excessive medical control with regard to antenatal screening. There is little evidence as to the preferences of Norwegian women regarding the actual screening process, but the number of scans has probably risen in recent years. Meanwhile, first-time mothers are getting older; their average age has increased from 25.3 to 28.1 during the course of the 15 years preceding 2005 (106). The prevalence of congenital anomalies such as Down syndrome is therefore likely to have gone up, but the number of abortions has nevertheless remained stable (14). The number of late abortions (after week 12) has increased gradually from 0.44 per 1 000 women in 1999 to 0.58 in 2006, 70% of which were carried out before week 18. The Medial Birth Registry cannot however, determine whether this trend can be ascribed to a higher frequency of scanning.

Equity of access

The routine ultrasound scan offered to Norwegian women in the second trimester is voluntary and – but for the co-payment charge – free. The uptake was 97,5% in 1994 (97), and participation is likely to remain high, judged by the number of scans carried out in the public sector. However, there is a lack of recent survey data on the national level with regard to the socio-economic, geographic or ethnic background of women with regard to utilisation of ultrasound scans, which could be used to address the issue of equity of access. However, based on statistics on utilisation and international research, it is possible to offer some

preliminary judgments with respect to geographic area. Norway is divided into four administrative health regions which are charged with offering specialist hospital services, including obstetric care to inhabitants. The dominant region, the South-eastern region, covers the densely populated area along the coastal stretch of southern Norway up to Oslo and its surrounding counties. More than half of all babies born in Norway in 2006 were delivered here, according to the figures (107) in the table below. Here, the rate is slightly higher than the national average of 2 scans per birth in the southeast. The rate is even higher in mid-Norway, the regional capital of which is Trondheim, where St Olav's Hospital, a renowned centre within the field of obstetrics and foetal medicine happens to be located, although no causality is implied. The lower than average rates are found in the two other regions, particularly in the sparsely populated and – in geographical terms – large Northern region – where for many, ultrasound facilities may be located miles away. For women living here, the offer of a first trimester scan could mean that they would have to make a long journey twice if the local hospital cannot provide such services. Such issues could however, to some extent be addressed by the use of telemedicine technology, especially with regard to anomalies such as serious congenital heart defects, as was demonstrated in a study from the UK (108) where scans for women in small towns in England were sent directly to perinatal cardiologists in London for detailed foetal echocardiography.

Table 16 Number of births and abdominal ultrasound scans, 2006

Regional Health Authority	Births	Per cent	Abdominal US scans	Per cent	Scans per birth
South-eastern	31 421	56	66 471	59	2.12
Western	12 806	23	21 960	19	1.71
Mid-Norway	7 270	13	17 140	15	2.36
Northern	4 854	9	7 638	7	1.57
Total	56 351	100	113 209	100	2.01

Source: The Norwegian Medical Birth Registry, and The Directorate of Labour and Welfare, 2006

In terms of the socio-economic status of those using ultrasound scans, research indicates (109;110) that utilisation may depend on socio-economic status and that screening uptake is higher among professional women compared to other groups. Ultrasound screening is to a

large extent publicly funded in Norway, and income distribution in Norway is relatively equitable. Implementation of first trimester universal scanning could actually improve equity of access, since the present system requires a woman not classified as “high risk” either to have a private scan or a referral from a general practitioner on the grounds of “medical anxiety” if she desires a first trimester scan. The hypothesis can as yet not be substantiated by domestic studies, but it is plausible to assume that well-informed, resourceful women are more likely to take advantage of such opportunities than other women. The level of co-payment, which would on average amount to NOK 560 per pregnancy, could provide a barrier to some groups, but there is an annual cap on co-payment for all public health services at around NOK 1 500 to ensure that low-income groups are not prevented from utilising services. In terms of ethnic minorities, Norway’s minority population has grown since 1994 when the survey on uptake was carried out and little is known as to whether the attitudes towards antenatal screening amongst minority groups differ from that of the overall population. Studies from Australia (111) and the Netherlands (112) indicate that there may be some variation according to uptake between ethnic groups. In 2005, about 5.7% of the resident population were born in countries outside the OECD, with Pakistan supplying the highest number of immigrants (113). Again, there is a need for further research to examine whether the utilisation rates differ compared to the overall population.

Ethical issues

Whether the Norwegian government chooses to expand its antenatal screening programme to include first trimester scanning or not, its action – or lack of such – will carry ethical implications (104). If the government were to recommend screening in the first trimester it would have to justify the move either in terms of medical gain or a reduction in spending. The systematic review conducted by Reinar *et al.* (15) concludes that the gains from ultrasound screening in the first trimester were marginal with regard to the determination of term date, multiple pregnancies or serious structural malformations without chromosomal anomalies. There are however, as has also been demonstrated by the present study, gains in terms of the detection of cases of Down syndrome. Even though the rate of scanning would remain the same following a potential reorganisation of provision as noted in a previous section, publicly funded first trimester scanning could increase the attention on anomalies such as Down syndrome. Implementing the programme could therefore be seen as reinforcing the negative attitude towards this condition, affecting people living with Down syndrome, other handicaps and prospective parents. This is seldom expressed in public, on the contrary, much is being

done, both in the medical field and in society at large, to enable people with Down syndrome and other serious conditions to enjoy life to its full potential, and to be integrated as much as possible in society. Some may argue however, that the subtext of antenatal screening programmes is that such people are not really welcome. Alison Davis, who has spina bifida, puts it bluntly (114) “I strongly believe that it is not possible to have a positive attitude towards a minority group while one is simultaneously directly involved in their deliberate destruction.” The fact that pregnant women are willing to avoid giving birth to an affected foetus by undergoing invasive procedures that could endanger an unaffected foetus underlines the point. However, the higher detection rates associated with a first trimester strategy is likely to enhance the opportunity to prevent the birth of children with Down syndrome, as happened in Denmark. Following the introduction of a first trimester combined risk assessment strategy the number of children born with the condition was virtually halved in that country (102). Solberg (104) ascribes this to the majority of women having access to early ultrasound, rather than a change in personal preferences towards having a child with Down. As in the case of economic studies, much of the attention paid to the ethics of antenatal screening refers to Down syndrome. The ethical picture may be somewhat different with respect to serious congenital heart defects due to the low survival rate – it may be easier to justify the removal of a foetus who is highly likely to die relatively soon after birth.

What if the government were to decide *not* to implement universal screening in the first trimester? The ethical impact of such a strategy would, according to Reinart *et al.* (15) be the following. Society would have to handle the costs arising from the birth of more children with anomalies or birth defects than would otherwise have been the case. It would further have to accept the potential burden for women who will have to bear an affected foetus for longer than “necessary” which involves more anxiety, or give birth to a child with an anomaly when this could have been avoided. Finally, it is suggested that to refrain from implementing first trimester universal scanning would be the same as to legitimise a limitation of the right of the individual to make choices in a private area in which real technological opportunities are offered. However, the availability of private screening implies that those who desire a first trimester scan would be able to have one if they could afford it.

It could however, not be entirely unreasonable to postulate that whatever course of action the government decides to take the ethical impact would be limited. There are at least two reasons for this: First: since “anxiety” was included as a medical indication for first trimester foetal

diagnostics in the guidelines for antenatal care of 2004 (104) women who do not necessarily fall into one of the defined risk groups may still request a scan for antenatal anomalies. One of the objectives of the Biotechnology Act of 2003 (17) was to avoid such cases, and an explicit distinction was made between genetic counselling and foetal diagnostics on the one side and routine ultrasound scanning on the other. The Act was intended to provide a bulwark against the so-called “society of qualitative selection - *sorteringssamfunnet*” – which has become something of a catchphrase in Norway (104). The distinction between foetal diagnostics and routine ultrasound may however, be hard to observe in practice or even in theory, and Solberg (104) notes that experts in the field of medicine were quick to point out that the law would not have any effect. Regardless of government policy, women can today do more or less whatever they want as far as first trimester screening is concerned. The fact that first trimester screening is on offer in the private sector means that potential parents will not be barred from undertaking the scan, unless they cannot afford it. To decide whether or not to have children is not primarily a medical issue, it is rather a matter to self-determination and autonomy (104). If women desire information about their foetus, they should be allowed to receive it. Sometimes the information is unwanted (115) though there may be a perceived social pressure by the very existence of the test, as noted by Forbes in New Zealand (98), which may lead to feelings of guilt if it were not utilised. Williams (116) describes the role of women going through ultrasound scanning in the first trimester as “moral pioneers”, in that they may have to make tough moral decisions.

Kvande (117) claims that the ethical debate surrounding obstetric ultrasound only surfaced in the 1990s and was largely suppressed in the first consensus conference on the issue in 1986. When it did arise, she argues, it was closely associated to the abortion issue and the development of technologies such as artificial insemination and so-called “designer babies” (118). Reinar *et al.* (15) argue that the ethics of antenatal screening has largely been left to the individual or to professional ethicists and that two fundamental values have not been questioned in the debate: Women’s right to choose abortion until the 12th week of gestation and the desire for a society where there is room for everyone. Hviid-Nilsen (119) calls the conflict between individual and collective desires the “state liberal dilemma” and compares it to Adam Smith’s theory of the invisible hand. In Smith’s theory, the sum of individual actions driven by self-interest served to benefit society as a whole. In the “state liberal dilemma” however, the sum of individual actions has an aggregate negative impact. Moreover individual actions do not take place in a moral void, as assumed in classical economics, but in

a situation where the state may sanction, even facilitate, the choices that collectively may constitute a burden.

Limitations

Outcome measures

The results presented in the previous chapter are those of a cost-effectiveness analysis where the outcome measure is the number of cases detected. For reasons outlined in the literature review, this is perhaps the most practical and straightforward approach with regard to examining the consequences of antenatal screening. However, this may also be the prime deficiency of this analysis. Though the point shall not be reiterated at length here, the literature review showed that detection might be associated with an economic value in itself, regardless of any subsequent action. Due to lack of data, the analysis cannot ascribe any such value to detection, and thus assist policymakers in determining whether this activity is worthwhile to extend in relation to other activities demanding resources within the health sector or in society as a whole. Further, the model only examines the number of anomalies found. Any advantages and disadvantages associated with the process of screening and diagnostic testing such as reassurance, anxiety and iatrogenic miscarriage are, in terms of their economic value, ignored. The same applies to any benefits that may be derived from the use of ultrasound in foetal medicine that could affect the health of the foetus or the mother. Again, as pointed out in the literature review, for all consequences to be compiled and valued, a cost-benefit or cost-utility analysis would have to be carried out. Such exercises would require data on either the Norwegian population's willingness to pay for - or the quality of life associated with - antenatal screening, which are currently unavailable.

The focus on anomalies may, given these constraints, not be entirely unreasonable. It is nevertheless restricted to covering only two. The original objective of this study, as stated in the protocol, was to include other anomalies in addition to Down syndrome and serious congenital heart disease. Effectiveness data on other anomalies were searched for, but it was difficult to find evidence that could be employed in the model. Either data were missing for both the first and second trimester, or the sample size in the efficacy study was too small. Moreover, the anomaly could be defined too broad in nature for the purpose of this study. An example of the latter is Saltvedt's study from 2006 (120), which looked at structural anomalies in chromosomally normal foetuses, but which included congenital heart disease in

their definition of structural anomaly. Nevertheless, the fact that the model comprises only two anomalies means that the results in terms of cost per anomaly detected and the difference in anomalies detected between the Current and the two other strategies may be somewhat distorted.

Efficacy data

Given the rapid technological development in this particular field, the efficacy data used in the model are relatively old. The actual sensitivity and specificity of the ultrasound scans used in Norwegian obstetrical clinics in 2006 may thus differ from those observed in the trials due to variations in standards of equipment. Even though the efficacy studies were picked out on the basis of geographic and chronological proximity, the skills level of the ultrasound operators could also deviate from that seen in clinical practice in 2006. This factor may have a significant impact on the outcome of the scan, according to Tegnander (71). Although the average age of the pregnant population has bearings on the risk for congenital anomalies, the data used have only been classified as “unselected” or “high risk”. The high-risk data used may not necessarily reflect the characteristics of the Norwegian group of women over the age of 38 or with a family history of congenital anomalies offered ultrasound in the first trimester as part of a system of foetal diagnostics.

The efficacy data used in the model are geared at measuring the number of cases that can be found of a single anomaly in either the first or second trimester, and are thus independent of each other, when in fact a population which has already been screened should be more “low-risk” than one which has not. However, the prevalence rate has been adjusted in the second trimester in the model to minimise the potential problems this could have caused. On the other hand, the model permits the detection of only one anomaly at a time, i.e. a case is labelled as either one with Down syndrome or serious congenital heart defects, when the two can in fact sometimes be linked to each other (1).

Costing

Except for the calculations of costs related to productivity loss, the costs used in the model are all based on tariffs. There are a number of drawbacks associated with this approach, since tariffs do not necessarily represent the opportunity costs of scarce resources. To elicit such costs in the context of antenatal screening, one should take account of the capital costs of the ultrasound scanners and foetal diagnostic equipment, the salaries of medical staff and the time

devoted to screening and diagnostic activities as well as a proportion of overhead costs to account of running costs and administration expenses (46). Such a task would however, be too time-consuming for the present study. Most of Norway's hospitals are state owned, but funding in 2006 was channelled through two sources, either directly through the Ministry of Health or indirectly via reimbursement tariffs from the National Insurance Administration. Outpatient activities were financed through the latter channel, and tariffs may thus be a useful proxy for costs in this area, provided that changes in the activity in question do not require major investments in buildings, capital or training. Nevertheless, the fact that the National Insurance Administration tariffs B20c and B20h - denoting routine abdominal or transvaginal ultrasound and counselling associated with antenatal diagnostics respectively - are perfectly identical, there is grounds for concern as to whether the tariffs are fully representative of the costs they intend to cover.

The use of market prices is a pragmatic attempt at mirroring the opportunity cost of production (46). Although it may be argued that the market for ultrasound scanning is not perfect due to factors such as asymmetry of information, it may be worthwhile to compare the prices advertised by ultrasound providers in the private sector to the tariffs used by public hospitals (46). It should be noted however, that private operators only seldom offer follow-up diagnostics and high-risk individuals tend to be referred to the public sector. A small, informal survey amongst private providers in Oslo revealed some variation in cost as seen in the table below. The prices are all more than 3 times the size of the National Insurance Administration tariff. Since the financing of outpatient services in public hospitals in Norway is only partly activity or tariff based, but also involves lump sum transfers, such services are in effect subsidized. It is therefore likely that the analysis of "full direct costs" described in the sensitivity analysis section of the last chapter would be closer to actual costs of ultrasound scanning in the public sector.

Table 17 Cost per ultrasound scan in the private sector, 2009-prices

Provider	Cost per scan, NOK	Comment
Ultralydklinikken (The Ultrasound Clinic)	900	3D ultrasound, operator not stated, includes DVD
Helsepartner (Health Partner)	700	Technology standard not known, scan conducted by paediatrician or radiologist
Volvat Medical Centre	1040	Technology standard not known, scan conducted by midwife

The issue of uncertainty surrounding the valuation of productivity loss in the calculation of indirect costs was raised in the last chapter. The time women spend away from work in the model is assumed to be the bare minimum. However, their partners might also take time off to accompany them. The parents might not be employed in paid work, but it is reasonable to assign some value to time, which could be spent in educational or leisure activities. Bricker *et al.*(67) have followed such an approach, but used a lower value for the non-work activities. This could not be done in the present model due to the lack of statistics on the daily activities of Norwegian pregnant women.

Model structure

The main advantage of the model structure is that it facilitates the overall probability of being found positive in the first stage of screening, while the detection rates of individual conditions may be presented separately in the results. It could easily be adapted to fit other types of screening tests where it is possible to detect several diseases based on one test, for example a blood or urine sample. However, certain assumptions may often have to be made to prevent the model from becoming too complex. There are two examples of such assumptions that could contribute to uncertainty regarding the results. The first relates to the modelling of follow-up diagnostics. As mentioned in the Results chapter, this is uniform across both anomalies and trimesters covered in the model. Although it is not possible to ascertain precisely the proportion of those testing positive for either anomaly that will proceed to follow-up testing, it seems intuitively reasonable to expect that the number for serious congenital heart disease is higher than that for Down syndromes. Moreover, the model suggests that if there were a 100% rate of follow-up, then some seven thousand amniocenteses would be conducted in Norway as a consequence of routine ultrasound scanning in the second trimester. The actual figure was 1100 in 2006. The reason for the disparity between the model and clinical practice could be one or more of the following: There are fewer women testing positive in the second trimester, the rate of follow-up in practice must be relatively low and that women testing positive may prefer another ultrasound scan rather than be confirmed by amniocentesis. The second element, somewhat linked to the first, concerns the modelling or rather lack of modelling of abortions – not the ones that occur as a consequence of antenatal screening, but rather prior to it. According to Svaasand (93), miscarriage takes place in 50% of all pregnancies with Down syndrome. As already mentioned this implies that the number of positive tests in both the first and the second trimester could be lower than in the model.

Leporrier however,(121) observes that detected cases of Down syndrome are more likely to be spontaneously aborted than undetected ones and since the model's outcome measure is detection, then the potential error might be reduced. Apart from reducing the number of potential scans, miscarriage or abortion would have an impact on the cost estimation in the model to the extent that it took place at a point between testing positive and follow-up diagnostics. The intrauterine deaths associated with serious congenital heart defects could not be ascertained.

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6 Conclusion

Summary of main findings

In 2006, the Government of Norway, via its Directorate of Health and Social Affairs, decided to investigate the consequences of a change in its policy with regard to the funding and provision of routine ultrasound scanning for pregnant women. The strategies that were to be specifically considered were two which included first trimester ultrasound scanning with nuchal translucency – with and without a serum test – in addition to the universal scan provided in the second trimester. The present study has considered the economic aspects of the proposed change, focusing on two serious congenital anomalies: Down syndrome and serious congenital heart defects, whilst acknowledging that there are other important outcomes which have not been captured in the analysis. The complex nature of antenatal screening and the many methodological challenges associated with economic evaluation in this field meant that a cost-effectiveness analysis was considered to be the most pragmatic and feasible approach. A cohort of 60 000 annual pregnancies was modelled in a decision tree, of which 5 000 were assigned to the so-called “high risk” group.

The primary objective of this analysis was to calculate the incremental cost-effectiveness in terms of cost per additional anomaly detected, from both the health care and societal perspective. It was found that incorporating first trimester universal ultrasound scanning enabled the number of total cases detected to increase by approximately 33% from 468 in the Current strategy to 620 in the Comprehensive strategy and 625 in the Combined strategy. The direct costs per additional case detected in the two first trimester universal scanning strategies were approximately NOK 218 000 (Comprehensive) and NOK 230 000, (Combined) while the total (direct + indirect) costs were approximately NOK 350 000 (Comprehensive) and NOK 398 000 (Combined). The Comprehensive strategy may be considered to be the most cost-effective of the two proposed first trimester universal scanning strategies, though the Combined strategy generates a few extra detected cases. In terms of average costs however, the Current strategy appears to be the most cost-effective choice with approximately NOK 71 thousand per case detected. An analysis of the breakdown of the extra cases detected showed that 77 (Comprehensive) and 82 (Combined) were cases of Down syndrome, whereas the remaining 543 in both strategies had serious congenital heart defects. This represents

approximately two thirds of the potential number of Down syndrome cases and about a quarter of the cases of serious congenital heart defects.

The secondary objective was to estimate the costs of the Current strategy, which was measured on the basis of 2006 tariffs (direct costs) and productivity loss (indirect costs). The direct costs were estimated to be NOK 33.2 million, while the total costs (direct + indirect costs) were NOK 68.8 million.

The number of cases confirmed as false positive rose by approximately 9% in the two first trimester universal scanning strategies. The sensitivity analyses showed that the rate of participation in follow-up diagnostic testing has a significant bearing on the results: Almost all Down syndrome cases could be found if the rate were 100%, and almost half of all cases of serious congenital heart defects. Increasing the rate of invasive testing however, is liable to cause a rise in the number of miscarriages.

Policy recommendations

It should be stressed that no decision with respect to extending the antenatal screening programme should be taken on the basis of economics alone, as there are significant ethical implications. Moreover, there is as yet no consensus as to how economic evaluations are to be interpreted. Outpatient services in public hospitals cost 6 481 million kroner in 2006 (122). Had a cost-benefit analysis been available, it might have shown that it would have been more sensible to spend the extra 33-36 million kroner on other health interventions, or even on programmes in other sectors, but no such analysis is available.

There are however, arguments in favour of a publicly financed first trimester universal scanning programme not necessarily related to the number of detected cases:

Resource planning: The private sector performs ultrasound scanning in the first trimester, but does not assume responsibility for follow-up diagnostic testing or counselling of those who test positive. These are referred to specialists in the public sector. In addition, statistics show that the public sector already funds on average 2 scans per pregnancy. If all pregnant women are offered a first trimester scan, early risk assessment may ensure that appropriate follow-up can be recommended for each woman. It is thus likely that a rationalisation of the

routine antenatal screening programme could reduce the extra expenditure associated with a first-trimester universal scanning component.

Women's preferences: Evidence from the literature and the emergence of private sector first trimester scanning provision suggest that women desire antenatal screening as early as possible in pregnancy, but they also demand appropriate information regarding how the scans are to be interpreted and the characteristics of follow-up testing.

Equity: First trimester scanning is privately offered to those who can afford it both within and outside Norway. The current system also enables women who are not strictly categorized as high risk to be referred to ultrasound scanning on the basis of pregnancy-related anxiety. Resourceful women might lobby their GP for such referrals, whereas less-informed women might not. A publicly financed first trimester universal scanning scheme would lower the potential barriers to access.

All other things equal, detection early seems intuitively to be better than detection late. The model shows that the Comprehensive strategy is the more cost-effective of the two proposed strategies, and is therefore the one that should be considered implemented first. There is however, some uncertainty as to the role of the serum test with regard to the need for follow-up testing, which should be investigated further.

The experience from Denmark and elsewhere suggests that increasing the role of the government in early antenatal screening can be interpreted as sanctioning a “qualitative selective society”. This is an issue not uniquely related to ultrasound screening, given the rapid development of other types of foetal diagnostics and the technology related to artificial insemination. However, it is recommended that the Government attempts to stress that a handicapped child should be as welcome as any other and can provide a valuable contribution to society. Perfection is not necessarily worth striving for.

Recommendations for further research

The economic literature on antenatal ultrasound screening shows that there is a great variation in cost estimates. It is therefore difficult to compare study results, even from the same country. There are no recent costing studies from Norway of the type carried out at Liverpool

Women's Hospital in the United Kingdom (123), and it is recommended that one be carried out in a representative hospital in this country to reveal the actual costs of ultrasound scanning and follow-up diagnostic tests. Furthermore, statistics should be collected as to the frequency and timing of ultrasound scanning among pregnant women. Combined, this information could be used to rationalise the public sector antenatal screening programme.

As to the need for further economic evaluation, this study has shown that there are challenges with regard to capturing all the potential positive and negative effects of ultrasound screening. The type of economic evaluation that could potentially capture all the dimensions of an antenatal screening programme is the cost-benefit analysis, though there are challenges with regard to its design and execution. A survey of willingness-to-pay for proposed strategies would have to be developed, but for such an analysis to be feasible, information should be made available as to what the consequences of different strategies would be in terms of how the detection and false positive rates at different stages in pregnancy and what this means to an average pregnant woman. The reason for this is that the willingness-to-pay may vary depending on not only on how many, but also what types of anomalies can be detected – lethal, a treatable condition or one involving long term morbidity. More information and transparency with regard to antenatal screening would be a good thing whether or not is to be used for an economic analysis. The co-ordinating role and information provided, both to the public, health personnel and researchers, by the United Kingdom's NHS Fetal Anomaly Ultrasound Screening Programme on its website (124) could provide a useful model. Moreover, since there seems to be no consensus as to the type of analysis best suited for antenatal screening and how it is to be interpreted, it is recommended that one ought to be found: Health economists and clinicians could set up a working group in order to propose a reference case, as, for example, done for economic evaluations of rheumatoid arthritis interventions by the OMERACT group (Outcome Measures in Rheumatoid Arthritis) (125)

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Appendix

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Figure A1 Model structure: Current strategy

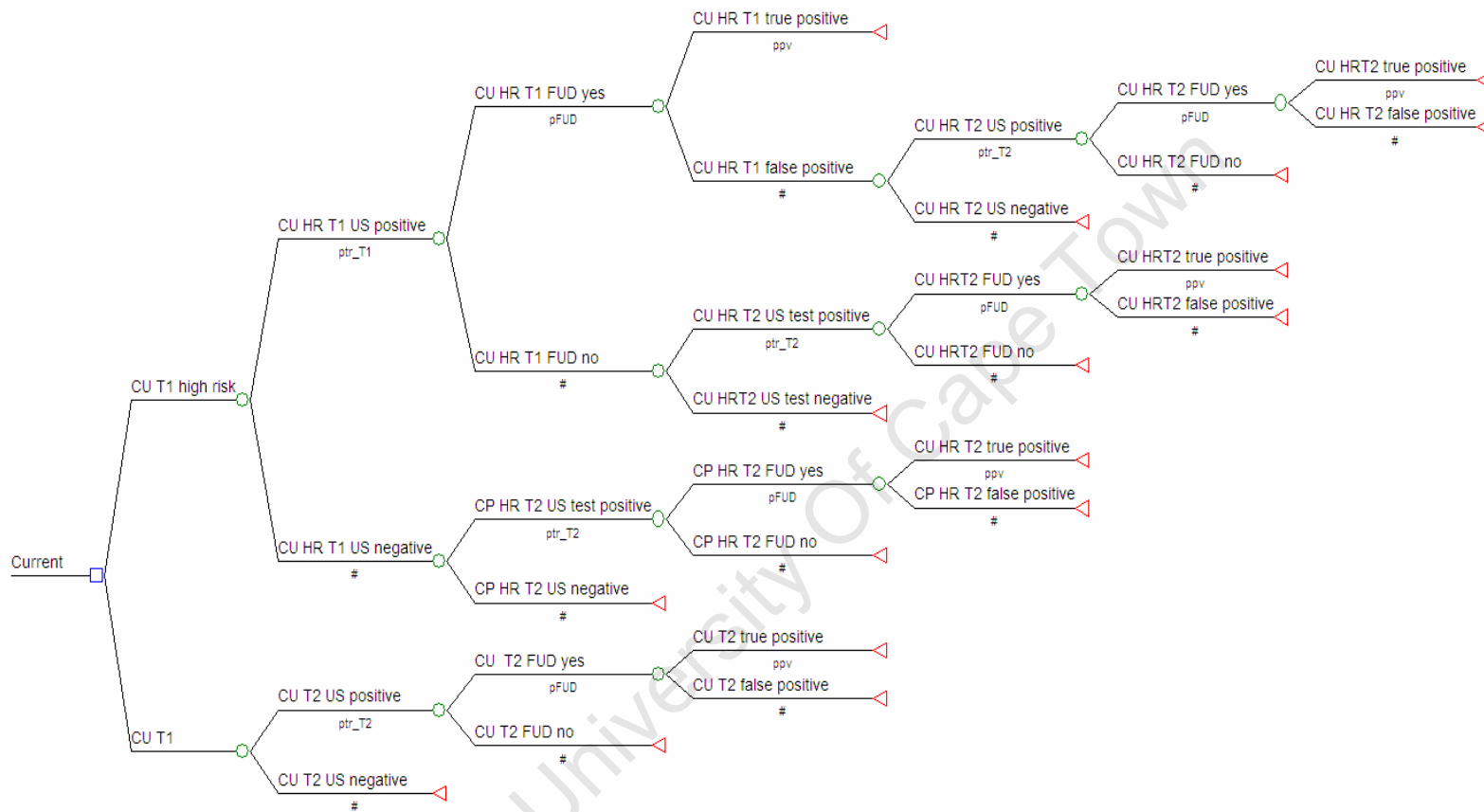


Figure A2 Model structure: Comprehensive strategy

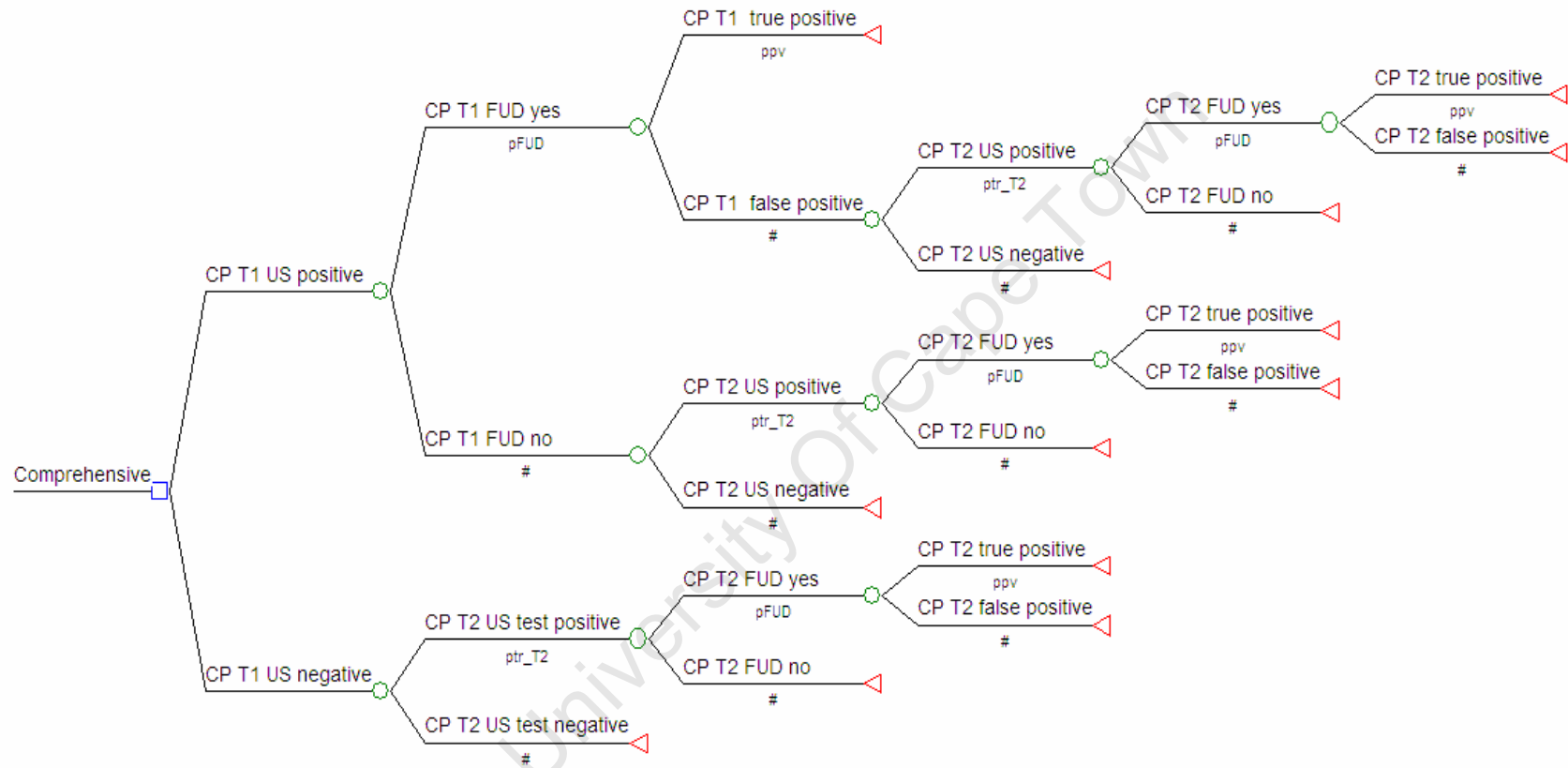


Figure A3 Model structure: Combined strategy

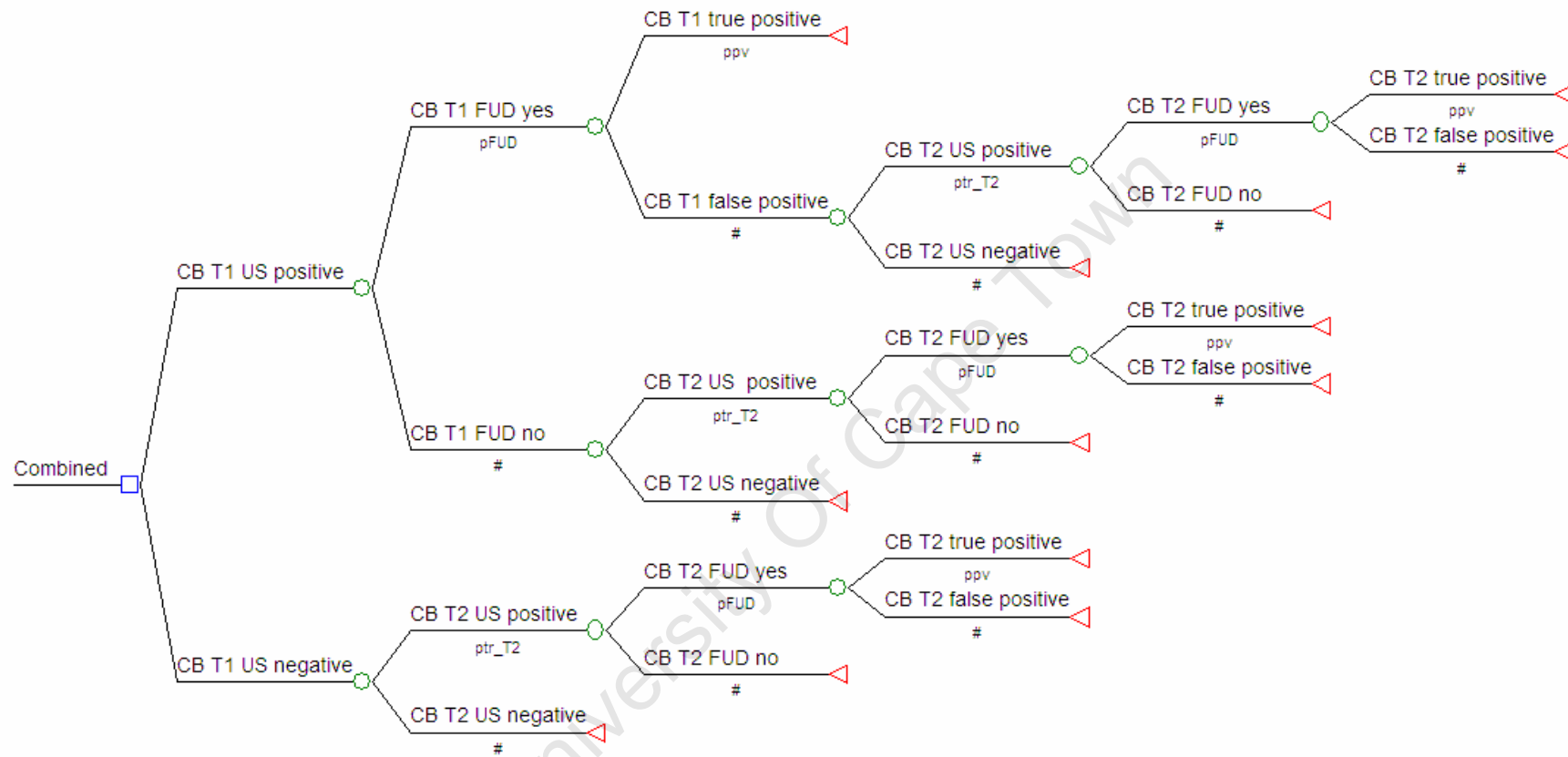
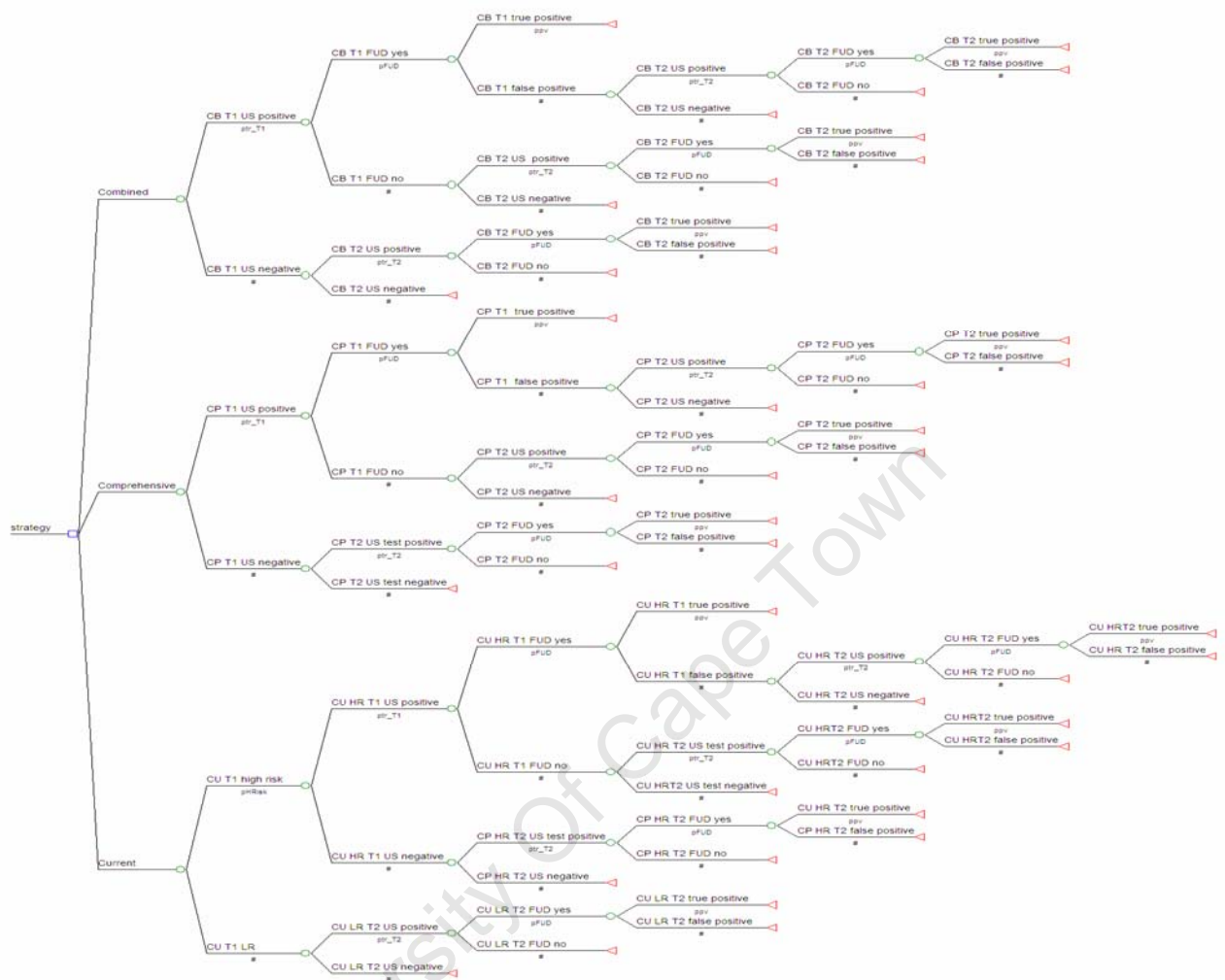


Figure A4 Entire model



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